28 June 2018
EMA/CHMP/391935/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Dexdor

International non-proprietary name: dexmedetomidine

Procedure No. EMEA/H/C/002268/II/0026

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
ASA	American Society of Anesthesiologists
CSR	Clinical study report
bpm	Beats per minute
DBP	Diastolic blood pressure
DEX	Dexmedetomidine
ECG	Electrocardiogram
EU	European Union
HR	Heart rate
FDA	Food and Drug Administration (USA)
ICU	Intensive care unit
IV	Intravenous
MAA	Marketing authorisation application
MAP	Mean arterial pressure
MDZ	Midazolam
OAA/S	Observer's Assessment of Alertness/Sedation Scale
PACU	Post anaesthesia care unit
PBO	Placebo
RD	Respiratory depression
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure
SpO2	Peripheral oxygen saturation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Orion Corporation submitted to the European Medicines Agency on 5 January 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include "For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation" for Dexdor; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.7, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 7.2.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	5 January 2018
Start of procedure:	27 January 2018
CHMP Rapporteur Assessment Report	29 March 2018
CHMP Co-Rapporteur Assessment Report	23 March 2018
PRAC Rapporteur Assessment Report	28 March 2018
Updated PRAC Rapporteur Assessment Report	6 April 2018
PRAC Outcome	12 April 2018
CHMP members comments	12, 16 and 17 April 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 April 2018
Request for supplementary information (RSI)	26 April 2018
PRAC Rapporteur Assessment Report	7 June 2018
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	13 June 2018
PRAC Outcome	14 June 2018
CHMP members comments	15 and 20 June 2018
Updated CHMP Rapporteur Assessment Report	21 June 20198
Opinion	28 June 2018

2. Scientific discussion

2.1. Introduction

Dexmedetomidine is an intravenously administered sedative agent that is currently approved in the European Union (EU) for sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3). Dexmedetomidine is an alpha-2 adrenoceptor agonist that exerts its sedative effects by acting on noradrenergic pathways originating in the locus coeruleus of the brain

stem, whereas benzodiazepine sedative agents act on GABAergic pathways. Because of its different mechanism of action, dexmedetomidine provides a somewhat different sedative profile. The MAH claims that patients sedated with dexmedetomidine are more rousable and able to communicate and yet remain calm and comfortable during mechanical ventilation.

In the central nervous system, many cardiovascular functions, arousal state, cognitive functions, nociception, body temperature, secretion of many hormones etc are under alpha-2 adrenergic regulation. In the periphery, alpha-2 adrenoceptors have a role in regulating functions such as smooth muscle tone, platelet aggregation, lipolysis, insulin secretion, and electrolyte secretion in the kidneys and intestines. Alpha-2 adrenoceptor activation therefore induces a characteristic pattern of pharmacodynamic responses that include dose-dependent sympatholysis (with reduction of blood pressure, heart rate and oxygen demand), sedation, analgesia, anxiolysis and anaesthetic/analgesic potentiation. These characteristics make alpha- 2 adrenergic agonists attractive for use in the perioperative and intensive care settings.

Dexmedetomidine 100 µg/ml (as the base) concentrate for solution is a simple aqueous solution for administration via the intravenous route. The final product is a sterile aqueous solution in vials and ampoules which is intended for dilution with a suitable solution prior to administration. It contains only dexmedetomidine hydrochloride, sodium chloride and water for injections.

The first worldwide approval of dexmedetomidine was in the USA in 1999 to Abbott Laboratories for short-term sedation (up to 24 hours) in the ICU. A further indication for procedural sedation was granted in the USA in 2008 to Hospira, which was at that time a strategic partner of Orion in many territories.

The marketing authorisation application (MAA) for ICU sedation had been considered not approvable when initially submitted to EMA in 2000 by Abbott. The Scientific Advice obtained at that time indicated two main concerns: that the clinical value of dexmedetomidine for ICU patients was not established and that the use of a loading dose at the start of treatment was not justified. After reacquiring the European rights to dexmedetomidine in 2005, Orion conducted two phase III trials to establish the clinical benefit of dexmedetomidine compared to propofol and midazolam in critically ill ICU patients. A new dosing scheme was incorporated in these studies, involving a wider dose range without the use of a loading dose. These two studies formed the basis for the approval of Dexdor for ICU sedation in the EU in 2011. Despite the procedural sedation indication being already approved elsewhere, Orion did not seek approval for this indication at that time, in order to concentrate on the use of dexmedetomidine in the ICU.

Orion is now submitting an application to update the ICU sedation indication for dexmedetomidine to include the procedural sedation indication. The additional indication proposed is: For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation. There is no change in the biopharmaceutics of Dexdor.

The proposed dosing recommendation for the procedural sedation is:

Initiation of Procedural Sedation:

- For adult patients: A loading infusion of 1.0 microgram/kg over 10 minutes.
- For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 micrograms/kg given over 10 minutes may be suitable.
- For awake fiberoptic intubation in adult patients: A loading infusion of 1 microgram/kg over 10 minutes.
- For patients over 65 years of age: A dose reduction should be considered.

Maintenance of Procedural Sedation:

- For adult patients: The maintenance infusion is generally initiated at 0.6 microgram/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.
- For awake fiberoptic intubation in adult patients: A maintenance infusion of 0.7 microgram/kg/hour is recommended until the endotracheal tube is secured.
- For patients over 65 years of age: A dose reduction should be considered.

Although there are many different potential clinical scenarios, the common objective for procedural sedation is to help patients tolerate uncomfortable or unpleasant conditions, often over a prolonged period, in a way that allows the procedure to be performed effectively and without risk from movement. It is also important to recognise that pain to a variable extent may be an important cause for patient discomfort during these procedures. Sedation does not ensure adequate pain relief and analgesia must therefore be considered as a separate issue.

Procedural sedation is not always restricted to a full anaesthesia / operating theatre environment but may be applied also in other settings, such as in a radiology department or an endoscopy clinic. In these settings in particular, administration of procedural sedation may be administered by non-anaesthetist physicians or other healthcare professionals. Practices differ across member states.

Propofol and benzodiazepines remain the most common sedative drugs used for procedural sedation, often in combination with local/regional anaesthesia and/or opioids. Ketamine can be used as a sole agent or as an adjunct, and differs by having a potent analgesic property.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

A Phase I environmental risk assessment has been performed and the assessment has been submitted. The Applicant has refined the Fpen given the likely treatment duration and the PECSURFACEWATER is well below the action limit. No further environmental risk assessment is required.

2.3. Clinical aspects

2.3.1. Introduction

This variation application is supported by two pivotal phase III, randomised, double-blind, placebo-controlled, multicentre clinical trials sponsored by Hospira. The MAC (2005-005) and AWAKE (2005-006) trials studied the use of dexmedetomidine in two distinct clinical situations. It is proposed to extrapolate the findings of these trials to the broader patient population of non-intubated adult patients for procedural sedation as defined by the proposed indication statement. In addition to the two main trials the application was supported by a review of literature, including two systematic

reviews which compare dexmedetomidine to propofol and to midazolam in several clinical scenarios in procedural sedation.

As with other agents used for procedural sedation under the control of an anaesthetist, the dose of dexmedetomidine requires careful individualised titration to achieve a safe and effective level of sedation. In the first marketing authorisation of dexmedetomidine in 1999 in the USA, the administration of dexmedetomidine for ICU sedation was recommended to be started with a loading dose of 1 mcg/kg followed by a maintenance dose of 0.2-0.7 mcg/kg/h. MAC and AWAKE trials were also planned and approved by FDA with an administration scheme starting with a loading dose. The aim, to establish a dexmedetomidine plasma concentration consistent with sedation, was safely achievable with a loading dose of 1 mcg/kg in 10 minutes infusion. In the MAC study, the loading dose was either 0.5 or 1 mcg/kg over 10 minutes. The 0.5 mcg/kg dose, recommended by the FDA, was added to allow the evaluation of safety and efficacy of a lower loading dose of dexmedetomidine, as well as aiding in preserving the study blind. The maintenance dose began at 0.6 mcg/kg/h and it was titrated in the range of 0.2-1 mcg/kg/h to achieve and/or maintain targeted sedation levels. In AWAKE, the loading dose of dexmedetomidine was 1 mcg/kg over 10 minutes, and the maintenance dose for dexmedetomidine was 0.7 mcg/kg/h. In literature reports, although both loading doses have been employed, the loading dose of 1 mcg/kg given over 10 minutes was more frequently used. Based on the clinical data presented by Abbott, Hospira and Orion, and the literature data, the use of loading dose of 1 mcg/kg within 10 minutes, or in 0.5 mcg/kg in 10 minutes for less invasive procedures such as ophthalmic surgery, followed with a maintenance dose of 0.2-1.0 mcg/kg/h or 0.7 mcg/kg/h for awake intubation has been evaluated.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The pivotal trials for this application were also submitted as supportive evidence in the original application for marketing authorisation for Dexdor and questions concerning GCP are therefore not pursued further in this procedure.

- Tabular overview of clinical studies

Table 1. Description of the phase III studies, MAC and AWAKE

Study No. of active centres/ country	Design Control type	Study & control drugs Dose, route and regimen	Duration of treat-ment	Rescue medication	Study objective	No. of patients by arm treated/ completed study drug	Primary endpoint
MAC (2005-005) 26 centres/ USA	Phase III, randomised, double-blind, PBO-controlled Randomised 2:2:1	DEX 0.5 mcg/kg loading dose over 10 min, maintenance infusion started at 0.6 mcg/kg/h, titrated to 0.2-1 mcg/kg/h; IV DEX 1 mcg/kg loading dose over	>30 min	MDZ for sedation: 0.5 mg IV bolus as needed to maintain OAA/S ≤ 4. Fentanyl for pain: 25	Safety and efficacy of DEX for sedation of patients requiring monitored anaesthesia care (MAC)	DEX 0.5 mcg/kg: 134/129 DEX 1 mcg/kg: 129/123	Percentage of patients not requiring MDZ for rescue sedation based on achieving and/or maintaining OAA/S ≤ 4.

		10 min, maintenance infusion same as above; IV PBO: 0.9% sodium chloride (saline); IV		mcg IV bolus as needed.		PBO: 63/57	
AWAKE (2005-006) 17 centres/ USA	Phase III, randomised, double-blind, PBO-controlled Randomised 1:1; stratified by Mallampati I-III vs. IV and ASA I-III vs. IV	DEX: 1 mcg/kg loading dose over 10 min, titrated to maintain 0.7 mcg/kg/h; IV PBO: 0.9% sodium chloride (saline); IV	30 min	MDZ for sedation: 0.5 mg IV bolus as needed to maintain RSS score ≥ 2.	Safety and efficacy of DEX for sedation during elective awake fiberoptic intubation	DEX 1 mcg/kg: 55/49 PBO: 50/46	Percentage of patients requiring rescue MDZ to achieve and/or maintain RSS score ≥ 2 throughout the study drug infusion.

PBO = Placebo; DEX = Dexmedetomidine; IV = intravenous : MDZ = midazolam; ASA = American Society of Anesthesiologists; OAA/S = Observer's Assessment of Alertness/Sedation Scale; RSS = Ramsay Sedation Scale; USA = United States

2.3.2. Pharmacokinetics

The MAC (2005-005) and AWAKE (2005-006) studies were designed to confirm the clinical safety and efficacy and no blood samples were taken for pharmacokinetic (PK) analyses in these studies. The previously submitted Dex-97-028 and W98-273 studies provide relevant PK data and the MAH refers to these to support the use of a loading dose of 1 µg/kg over 10 min.

DEX-97-028

Objectives: The primary objectives were to identify the dose–exposure relationship for sedation using single IV doses of dexmedetomidine; to select and include 3 doses for the long-term infusion portion of Part II; and to investigate the effects of long-term infusions (12- and 24-hour) of dexmedetomidine on the sedative profile compared with single doses.

Study Design: During the each part of the study, healthy volunteers received dexmedetomidine or placebo as a 2-stage infusion regimen (loading and maintenance). The target steady state concentrations and dexmedetomidine administration rates are presented in Table below.

Table 1 Dexmedetomidine administration rates

Target steady state (ng/ml)	Part I 1 h infusion		Part II 12 h infusion		Part II 24 h infusion	
	10 min loading infusion (mcg/kg/h)	50 min maintenance infusion (mcg/kg/h)	10 min loading infusion (mcg/kg/h)	≤ 12 h maintenance infusion (mcg/kg/h)	10 min loading infusion (mcg/kg/h)	≤ 24 h maintenance infusion (mcg/kg/h)
0.1	1.00	0.056				
0.3	3.00	0.168	3.00	0.168	3.00	0.168
0.45	4.50	0.252				

0.6	6.00	0.337		6.00	0.337
1.25[a]	3.70	1.00		3.70	0.700

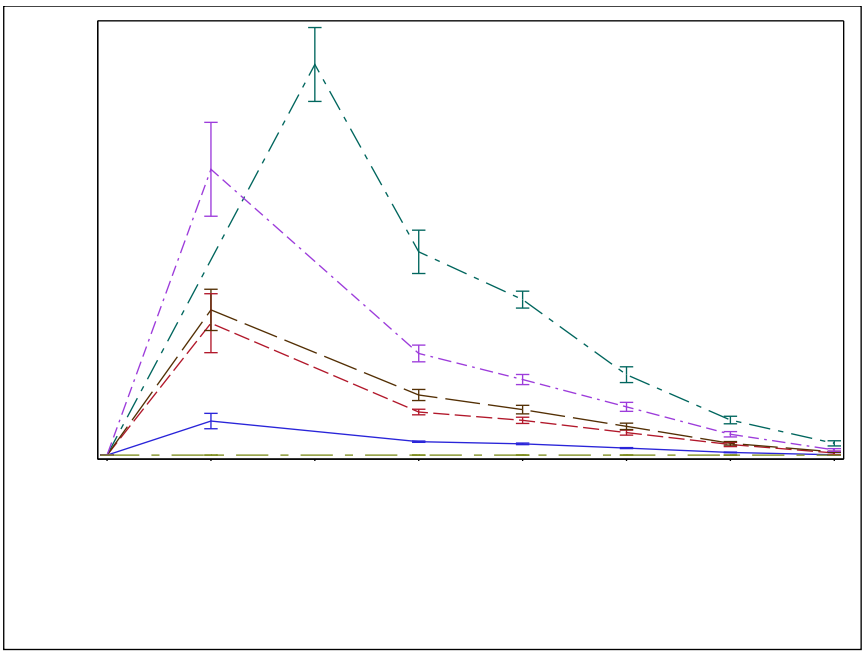
[a] During the 1-hour and 24-hour infusions, a 35-minute loading infusion was used.

Source: DEX-97-028 CSR Table 5.4.1a

Mean dexmedetomidine plasma concentrations after a 10-min loading dose of 1.0 µg/kg (6 µg/kg/h) were 1.8 ng/ml in part I and 1.1 ng/ml in part II. Mean concentrations following the 10-min loading infusion in part II were lower than in part I due to that actual sampling time point was slightly later than 10 minutes.

Results: The relationship of dose time-concentration relationship is given in Figure below. The mean dexmedetomidine plasma concentrations after a 10-min loading dose of 1.0 µg/kg (6 µg/kg/h) were 1.8 ng/ml in part I and 1.1 ng/ml in part II, respectively (see Table below). According to the Applicant the mean concentrations following the 10-min loading infusion in part II were lower than in part I due to that actual sampling time point was slightly later than 10 minutes.

Figure 1 Mean dexmedetomidine plasma concentrations vs. time profiles; after loading doses followed by a 50-minute maintenance infusions



At the infusion rate 3.7 µg/kg/h 35-minute loading infusion was used

Table 2 Mean dexmedetomidine plasma concentrations following 10 min loading inf., N = 6

Concentrations (ng/ml)	10 min loading infusion								
	1.0 mcg/kg/h	3.0 mcg/kg/h			4.5 mcg/kg/h	6.0 mcg/kg/h		3.70[a] mcg/kg/h	
	Part I	Part I	Part II[b]	Part II	Part I	Part I	Part II	Part I	Part II
Mean (±SD)	0.2 (±0.1)	0.8 (±0.4)	0.5 (±0.1)	0.5 (±0.04)	0.9 (±0.3)	1.8 (±0.7)	1.1 (±0.3)	2.4 (±0.6)	2.4 (±0.6)
Max	0.4	1.2	0.6	0.6	1.2	2.7	1.4	3.3	3.3
Min	0.1	0.2	0.4	0.5	0.4	0.8	0.7	1.7	1.4

SD = standard deviation

[a] plasma concentration following 35-min loading infusion

[b] plasma concentration following 10-min loading infusion (total infusion time 12 h)

W98-273

Similar results were obtained in study W98-273 in Japanese subjects (n=6); after a 10 min loading infusion (6 µg/kg/h) the mean ± SD plasma concentration was in the range 1.5-1.9±1 ng/mL.

Summary

Doses in the range 0.2-1.4 µg/kg/h are recommended in the SmPC for ICU sedation. For ICU sedation patients, a maintenance infusion rate of 0.95 µg/kg/h and 1.4 µg/kg/h are expected to result in mean steady-state plasma concentrations of approximately 1.72 ng/mL and 2.33 ng/mL, respectively (Study 3005012 Prodex, Study 3005013 Midex). The mean concentrations reached by the loading infusion are at the same level as the mean steady state plasma concentration after a dose of 0.95 µg/kg/h.

Based on above, the Applicant draws the conclusion that dexmedetomidine plasma concentration needed for sedation is achievable with a loading dose of 1 µg/kg over 10 minutes.

Specific PK considerations for the current application

There are a number of important differences in the PK considerations for the new compared to the existing indication.

Firstly, the situation is somewhat simplified by the fact that the new target patient population is rather less likely than the currently approved ICU population to have highly variable and unpredictable drug handling as a result of various disturbance in physiology associated with critical illness. Hence PK data in healthy adults can be more directly applied to the new patient population.

Secondly, the time taken for the effects of the sedative drug to wear off is of far greater importance in the new target patient population. In the ICU this is usually not very relevant, but a high percentage of procedures requiring sedation are done as day cases so patients need to be fully recovered in a short time frame so that they can go home.

PK aspects relevant to onset of effect

Dex-97-028 and W98-273 studies summarise the PK data that support the use of a 10-minute loading infusion at 6 mcg/kg/h that is equivalent to a loading dose of 1 mcg/kg over 10 min.

The mean plasma concentration achieved by the loading infusion 1 mcg/kg infused over 10 minutes was about 1.8 ng/ml. Doses 0.2-1.4 mcg/kg/h are recommended in the SmPC for ICU sedation. For ICU sedation patients, a maintenance infusion rate of 0.95 mcg/kg/h and 1.4 mcg/kg/h are expected to result in mean steady-state plasma concentrations of approximately 1.72 ng/ml and 2.33 ng/ml, respectively (3005012 Prodex, 3005013 Midex). The mean concentrations reached by the loading infusion are at the same level as the mean steady state plasma concentration after a dose of 0.95 mcg/kg/h.

Based on above, the MAH argued that dexmedetomidine plasma concentration needed for sedation is achievable with a loading dose of 1 mcg/kg over 10 minutes.

PK aspects relevant to offset of effect

The time taken to achieve full reversal of sedation is an important consideration for procedural

sedation, especially for procedures performed as day cases. A number of PK parameters are important in this context including short term drug re-distribution and clearance.

2.3.3. Pharmacodynamics

Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. Unlike other sedative agents used in standard of care and acting as GABA receptor antagonists (e.g. midazolam, propofol), its effects are claimed to be mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem conferring a mechanism of arousal and different form of sedation.

The SmPC for Dexdor states that as well as sedative and sympatholytic effects, dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects and is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects. The MAH states that it produces a state of 'cooperative sedation', allowing the patient to interact with healthcare providers (Unger et al 2006, Pandharipande et al 2006). While patient cooperation can be achieved with other sedatives properly dosed, dexmedetomidine maintains this property throughout the usual dosage (Gerlach et al 2007). The characteristics of cooperative sedation are highly desirable in the outpatient surgery population where patients are expected to be discharged home safely and shortly after their surgery. The MAH further argued that because of its pharmacodynamic properties, dexmedetomidine appears to address many of the needs of IV sedation in non-intubated patients undergoing surgical and other procedures.

It is agreed that no further pharmacodynamic data are necessary to support the claimed new indication. The pharmacodynamic mechanism is essentially the same and there are no new secondary pharmacodynamic considerations.

2.3.4. Discussion on clinical pharmacology

No new PK or PK/PD modelling data have been submitted in the present application. This could in general be acceptable, however some SmPC recommendations need to be improved that could be solved with PK/PD modelling, such as a dose reduction in elderly patients and better defining the recovery phase. The MAH could use available PK/PD data and use of modelling and simulation.

The MAH was requested to further discuss the PK characteristic of DEX in the context of the relatively slow recovery time observed for DEX in the MAC trial. The responses were satisfactory.

2.3.5. Conclusions on clinical pharmacology

The CHMP considers the submitted clinical pharmacology data sufficient.

2.4. Clinical efficacy

The evidence of efficacy for the proposed new indication comes primarily from two phase III randomised, double-blind, placebo-controlled, multicentre studies MAC (2005-005) and AWAKE (2005-006), in in non-intubated patients requiring sedation. These two trials are supplemented with an extended review and analysis of literature.

The **MAC study (2005-005)** evaluated dexmedetomidine for sedation under the control of an anaesthetist in 326 patients undergoing surgery under local or regional anaesthesia. It was conducted at 26 investigative sites in the USA and enrolled a broad range of patients scheduled for a variety of elective surgical procedures including orthopaedic, ophthalmic, plastic, vascular, breast biopsies and excision of lesions. The objectives of sedation in this clinical situation are conscious sedation, comfort, analgesia, anxiety control and overall patient satisfaction, with acceptable safety especially in relation to cardiovascular and respiratory depression. For some procedures it may also be necessary for the patient to respond purposefully to verbal input.

The **AWAKE study (2005-006)** evaluated dexmedetomidine for awake fibreoptic oral or nasal intubation prior to a surgical or diagnostic procedure in 105 patients expected to be difficult to intubate. It was conducted at 17 investigative sites in the USA. Awake intubation in a patient with a potentially difficult airway is an extremely stimulating procedure that may be associated with large haemodynamic changes. To attenuate this response, blunting of the airway reflexes is required without losing the cooperation of the patient. A successful awake fibreoptic intubation requires an anaesthetist experienced in this technique, adequate topical anaesthesia of the airway, and a sedated yet cooperative patient. The most common complications of this procedure are hypoxemia and gastric content aspiration. Benzodiazepines, combined with opioids, are commonly used for anxiolysis and/or analgesia during awake fiberoptic intubations. Unfortunately, this combination of drugs can cause respiratory depression, placing the patient at risk for hypoxemia and aspiration.

Measurement of sedation

Sedation with dexmedetomidine has been documented using several validated assessment tools. In the MAC study, the Observer's Assessment of Alertness/Sedation Scale (OAA/S) was selected as the intraoperative sedation scale as it was considered suitable for the non-intubated patient population undergoing monitored anaesthesia care. This measure has been used and validated in the perioperative and postoperative settings (Chernik et al 1990). The target sedation level was OAA/S ≤ 4, (lethargic response to name, mildly slow speech, eyes glazed or mild ptosis).

Definition of Observer's Assessment of Alertness/Sedation (OAA/S) scale

Responsiveness	**Speech**	**Facial expression**	**Eyes**	**Composite score**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild				1

prodding or shaking				(deep sleep)

Reference: Chernik et al 1990

In the AWAKE study, the Ramsay Sedation Scale (RSS) was used to determine the level of sedation. The RSS has been used and validated in intubated and non-intubated patients in operating room settings (De Jonghe et al 2000). The target sedation level was RSS ≤ 2 (cooperative, oriented, tranquil).

Definition of Ramsay Sedation Scale (RSS)

Sedation score	**Clinical response**
1	Subject is anxious and agitated or restless, or both
2	Subject is cooperative, oriented and tranquil
3	Subject responds to command only
4	Subject exhibits brisk response to light glabellar (between the eyebrows) tap or loud auditory stimulus
5	Subject exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Subject exhibits no response to stimulus

Reference: De Jonghe et al 2000

Main study MAC (2005-005)

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Dexmedetomidine for Sedation During Monitored Anaesthesia Care (MAC)

Methods

This was a Phase III, randomized, double-blind, placebo (PBO)-controlled, multicentre study designed to evaluate the safety and efficacy of DEX when used for sedation of subjects requiring MAC for elective surgery or a procedure.

A broad range of patients scheduled for a variety of elective surgeries/procedures performed in an operating room (OR) or procedure room with an anaesthetist in attendance was tested. The types of surgeries/procedures included in this study were: orthopaedic, ophthalmic, plastic, vascular stents, breast biopsies, AV fistulas and excision of lesions. Surgeries/procedures were expected to take longer than 30 minutes to complete. An estimated 325 subjects (130 DEX 0.5 mcg/kg load, 130 DEX 1 mcg/kg load, 65 PBO) were to be randomized at 26 investigative sites.

Subjects were screened up to 14 days prior to receiving study drug infusion. During screening subjects were assessed for eligibility (inclusion/exclusion criteria), a physical examination was performed and a medical history was taken. If a 12-lead electrocardiogram (ECG) was performed at this time, it did not

have to be repeated at baseline. Informed consent was obtained prior to the performance of any study-specific procedures.

At baseline, prior to study drug infusion, eligible subjects were randomized in a 2:2:1 ratio (DEX 0.5 mcg/kg load: DEX 1 mcg/kg load: PBO) in 1 of 3 blinded arms of the study. Randomisation was stratified by surgery/procedure type. Subjects were fitted with standard monitors for ECG monitoring, blood pressure (BP), heart rate (HR), respiratory rate (RR), and pulse oximetry (SpO2). If not obtained at screening, a 12-lead ECG was obtained at this time and a baseline Observer's Assessment of Alertness/Sedation scale (OAA/S) score was obtained and recorded. Blood samples for baseline laboratory assessments were collected. For female subjects of childbearing potential, a urine pregnancy test was performed to confirm eligibility.

Following completion of baseline procedures, blinded study drug infusion began. Subjects received a loading dose of study drug administered over 10 minutes (DEX 0.5 mcg/kg, DEX 1 mcg/kg, or placebo). Following completion of the load, the maintenance infusion was started (initiated at DEX 0.6 mcg/kg/hr for all subjects randomized to receive DEX; and PBO for all subjects randomized to receive PBO).

The level of sedation was assessed during study drug infusion and during the subject's stay in the Post-Anesthesia Care Unit (PACU) using the OAA/S. The first OAA/S score during the Double-Blind Treatment Period was evaluated and recorded 15 minutes following the start of study drug infusion. After that, OAA/S scores were obtained every five minutes throughout the remainder of study drug infusion. Whenever possible, the same investigator or designee obtained OAA/S scores throughout the study for a given subject.

The target OAA/S score during study drug infusion was ≤ 4 (lethargic response to name, mildly slow speech, eyes glazed or mild ptosis). After the first 15 minutes of study drug infusion, study drug could be titrated in order to achieve and/or maintain an OAA/S of < 4, and if necessary, rescue MDZ was administered. For subjects with an OAA/S score of < 3 (over-sedated) the maintenance study drug infusion rate was decreased to a minimum of 0.2 mcg/kg/hr for DEX (or an equivalent rate for placebo).

For subjects with an OAA/S score > 4 (not sedated) the investigator was encouraged to achieve sedation by increasing the maintenance study drug infusion rate to a maximum of 1 mcg/kg/hr for DEX (or an equivalent rate for placebo) prior to giving rescue medication. After titration to a maximum infusion rate, the investigator could administer rescue MDZ (0.5 mg IV) as needed to achieve sedation. Rescue MDZ was not administered if the OAA/S score was ≤ 4. All subjects enrolled in the study received a local anaesthetic block prior to surgery/ procedure. The block was performed at least 15 minutes after the beginning of study drug infusion when an OAA/S score ≤ 4 was observed. Local anaesthetic infiltration extended 1 dermatome above and below the site of incision and surgery. The extent of the anaesthetic block was recorded by sensory dermatome section on the Case Report Form (CRF). The ophthalmic surgeon or anaesthesiologist performed retrobulbar blocks when indicated for eye surgery; and the anaesthesiologist performed axillary blocks, interscalene blocks or selective nerve blocks when indicated. No spinal or epidural anesthesia was permitted in this study. The local anaesthetic solution, concentration and volume were recorded. The study drug maintenance infusion was continued during the local anaesthetic block. An OAA/S score ≤ 4 was required prior to entry into the operating room (OR)/procedure room as well as prior to the time the local anaesthetic block was administered.

If, after the first 15 minutes of study drug infusion, pain was present, the investigator could administer rescue fentanyl (25 mcg IV). Every dose of fentanyl that was given was justified as fitting into 1 of the following 2 categories and was recorded as such on the CRF:

- Subject expressed that his/her pain score was > 3 on a scale of 0-10, where 0 was no pain and 10 was the worst pain ever experienced.
- Verbal communication was not possible – presence of pain was based on the investigator's judgment.

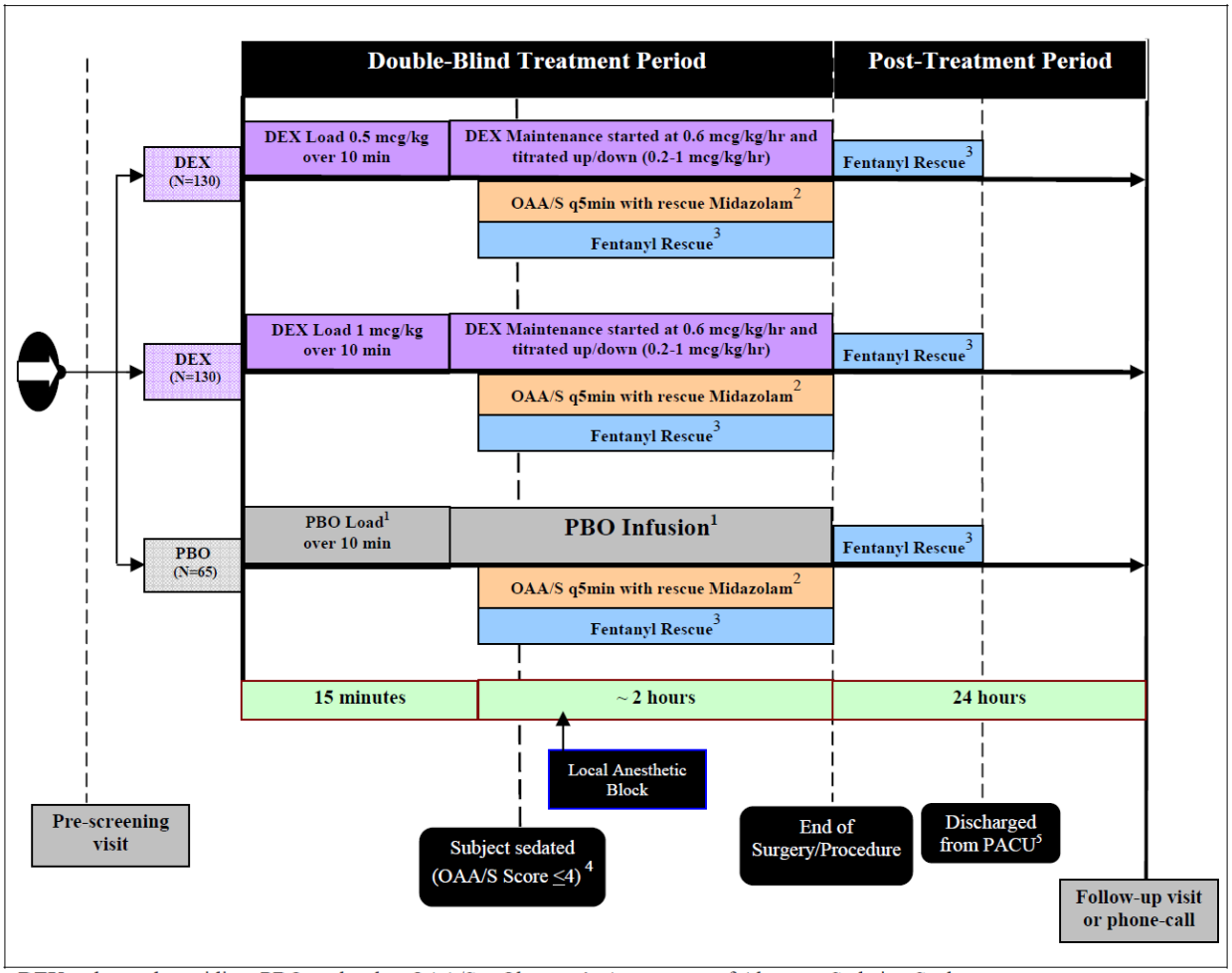
No rescue medication (MDZ or fentanyl) was administered during the first 15 minutes of study drug administration.

During the Double-Blind Treatment Period the following was recorded every 5 minutes: systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, RR, SpO2, and OAA/S. Cardiac monitoring was continuous. The amounts of rescue fentanyl and MDZ administered were also recorded. During surgery/procedure, subjects could have nasal cannula oxygen at 3 litres/min or per practice standard at each site. Immediately prior to transfer of the subject to the PACU, study drug infusion was discontinued. Subjects remained in the PACU for a minimum of 1 hour following discontinuation of study drug.

After the subject arrived in the PACU, the anaesthetist responded to questions related to the ease of maintenance of appropriate intraoperative sedation, respiratory stability, haemodynamic stability and subject cooperation using Visual Analog Scales (VASs).

Upon arrival in the PACU, vital signs and SpO2 were recorded every 5 minutes for the first 15 minutes, then every 15 minutes for the next 45 minutes. OAA/S, pain scale and Aldrete scores were assessed every 15 minutes while the subject was in the PACU. A 12-lead ECG was performed and cardiac monitoring was continuous. The PACU nurse administered fentanyl boluses (25 mcg IV) in response to a subject pain score $\geq$ 4, or, if verbal communication was not possible, when pain was judged to be present by the investigator. Readiness for discharge was evaluated using site-specific criteria and the Aldrete Scoring System. The time from discontinuation of study drug to achievement of an Aldrete score $\geq$ 9 was recorded for each subject.

Subjects were discharged when the site-specific PACU criteria were satisfied and the Aldrete Score was $\geq$ 9. A blood sample for postoperative laboratory assessments was obtained prior to discharge from the PACU. Subjects were visited or contacted by telephone 24 hours after the discontinuation of study drug to assess satisfaction with the sedation using the Iowa Satisfaction with Anesthesia Scale (ISAS) and the level of anxiety experienced before, during and after the study drug infusion process using the Anxiety Assessment Scale.



DEX = dexmedetomidine; PBO = placebo; OAA/S = Observer's Assessment of Alertness Sedation Scale
[1]PBO group received sodium chloride at an infusion rate equivalent to the DEX group.
[2]Beginning 15 minutes after start of study drug infusion, and continuing throughout the surgery/procedure, rescue boluses of MDZ (0.5 mg) were given if OAA/S was >4 after titration of study drug.
[3]Beginning 15 minutes after study drug infusion, until subject was discharged from the PACU, rescue boluses of fentanyl (25 mcg IV) were given as needed for pain based on protocol-specified pain assessments.
[4]The subject was sedated (OAA/S ≤ 4) prior to entry into the operating room, procedure room, or block room and prior to administration of local anesthetic block.
[5]At least one hour after study drug had been discontinued.

Choice of control groups

The MAH states that this study was designed to evaluate the safety and efficacy of DEX when used for sedation of subjects for elective surgery or a procedure, in comparison with a blinded saline PBO control. The protocol-specified dose of DEX was selected based on the literature reports and recommendations from expert advisors. As recommended by the FDA, a low dose loading arm (DEX 0.5 mcg/kg) was added to the study "in order to aid in preserving the study blind" and to "establish a benchmark".

Study participants

Male or female subjects requiring Monitored Anaesthesia Care (MAC) for elective surgery/procedure expected to take longer than 30 minutes and performed under local anaesthetic block, and meeting the inclusion and exclusion criteria below, were selected and screened for enrolment. In line with FDA

recommendation the trial covered a broad range of surgical procedures including orthopaedics, podiatry, ophthalmology, gynaecology, urology, general surgery, and vascular procedures.

Key Inclusion Criteria

- Any age >18, any fitness for anaesthesia (ASA grade I to IV), no pregnancy possibility.

Key Exclusion Criteria

- Need for endotracheal intubation or laryngeal mask airway or epidural or spinal anaesthesia.
- Recent general anaesthesia or alpha-2-agonist, opioid within 4 hours, recent MI or unstable angina. Otherwise no restriction on prior and concomitant therapy.
- Specified CNS or psychiatric disease, abnormal liver function.

Participation in the study could be terminated by the subject, the investigator, or Hospira at any time. Subjects could be discontinued from study drug infusion for various standard reasons relating to ethics, GCP and patient welfare, and in particular if the subject could not be adequately sedated by protocol-allowed amounts of study drug and rescue medication. Subjects who prematurely discontinued were not replaced. The date and reason for premature discontinuation was recorded on the appropriate CRF.

Treatments

Study drug was infused using a controlled infusion device such as a standard intravenous infusion pump system. Study drug was not rapidly bloused.

The investigational drug was DEX injection (100 mcg/mL, base). The PBO control was 0.9% sodium chloride. The sponsor supplied the investigative sites with the DEX for infusion. Blinded study drug was prepared (diluted) by the site pharmacy. Blinded study drug was administered as a two-stage infusion:

- a 10-minute loading dose infusion of either DEX or PBO
- a maintenance dose infusion of DEX or PBO

For the subjects randomized to receive a 0.5 mcg/kg DEX loading dose, the loading infusion bag DEX concentration and the maintenance infusion bag DEX concentration were 4 mcg/mL. For the subjects randomized to receive a 1 mcg/kg DEX loading dose, the loading infusion bag DEX concentration was 8 mcg/mL and the maintenance infusion bag DEX concentration was 4 mcg/mL.

All subjects received a loading dose volume of 0.125 mL/kg administered over 10 minutes, regardless of treatment group. DEX maintenance infusion began at a rate of 0.6 mcg/kg/hr and was titrated up or down (between 0.2 mcg/kg/hr and 1 mcg/kg/hr) as required to achieve and/or maintain Observer's Assessment of Alertness/Sedation (OAA/S) score ≤ 4.

Midazolam

If a subject was not adequately sedated (OAA/S score > 4) through titration with randomized study drug, MDZ could be administered. Rescue MDZ could be administered only after attempting to achieve sedation using study drug. Rescue MDZ was given as single bolus doses of 0.5 mg IV, repeated as needed to achieve an OAA/S score of ≤ 4. An OAA/S score was obtained before the administration of

any rescue MDZ medication. Rescue MDZ was not administered if the OAA/S score was ≤ 4. The timing, dose and reason for use of MDZ were recorded on the CRF.

Fentanyl

Rescue boluses of fentanyl (25 mcg IV) could be given in the presence of pain. For every dose of fentanyl given, a justification fitting 1 of the following 2 categories applied and was recorded on the CRF:

- Subject expressed that his/her pain score was > 3 during study drug infusion and > 4 in the PACU on a scale of 0-10, where 0 was no pain and 10 was the worst pain ever experienced.
- Verbal communication was not possible – presence of pain based on the investigator's judgment.

The timing, dose and reason for use of fentanyl were recorded on the CRF.

At any time clinically indicated (e.g., subject discomfort despite maximum doses of study drug and rescue), at the discretion of the anaesthetist, the subject was converted to an alternative sedative and/or anaesthetic therapy. If a subject was converted to an alternative sedative and/or anaesthetic therapy, study drug was discontinued.

Objectives

The primary endpoint was the percent of subjects not requiring MDZ for rescue sedation based on achieving and/or maintaining an OAA/S score ≤ 4. This primary endpoint was selected to establish DEX as a stand-alone sedative/anxiolytic.

Secondary efficacy variables were:

- The total amount (mg) of rescue midazolam required to achieve and/or maintain sedation (OAA/S score ≤ 4).
- Time from onset of study drug infusion to first dose of rescue MDZ.
- Percentage of subjects who converted to alternative sedative and/or anaesthetic therapy due to failure of treatment with study drug and rescue.
- Time to recovery and readiness for discharge from PACU: assessed by time from discontinuation of study drug to reach Aldrete score ≥ 9.
- Total amount of fentanyl required for pain control.
- Anaesthetist assessment of ease of management; subject cooperation.
- Incidence of post-operative nausea and vomiting (PONV) in PACU.
- Overall subject satisfaction and anxiety assessed 24 hours after study drug had been discontinued.

Three analysis datasets were defined for data analysis, the safety dataset, the intent-to-treat (ITT) dataset, and the per protocol (PP) dataset. The safety dataset consisted of all subjects who received study drug. The ITT dataset consisted of all subjects who received the randomized study drug and had at least one post-baseline efficacy measure recorded. The PP dataset consisted of all subjects in the

ITT dataset excluding those who had improper dosing of study medication, had used prohibited concomitant medications, and had other major protocol violations. The PP dataset was approved by the sponsor prior to breaking the randomization codes.

Outcomes/endpoints

The intraoperative sedation scale used to measure of depth of sedation in the trial was the Observer Assessment of Alertness/Sedation Scale (OAA/S). This measure has been used and validated in perioperative and postoperative patients (Chernik DA, Gillings D, Laine H, Hendler J, Silver J, Davidson A, Schwam E, Siegel J. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. Journal of Clinical Psychopharmacology 1990:10:4:244-251).

Prior to the start of study drug infusion, the investigator or designee obtained a baseline score on the OAA/S. Whenever possible, the same investigator or designee obtained OAA/S scores every 5 minutes throughout the study drug infusion, beginning 15 minutes after the start of infusion, and every 15 minutes while the subject was in the PACU. Table 8 lists the OAA/S criteria. An OAA/S score also was obtained prior to the administration of any rescue MDZ.

Table 8 Observer's Assessment of Alertness/Sedation (OAA/S)

Assessment Categories				
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	--	--	2
Does not respond to mild prodding or shaking	--	--	--	1 (deep sleep)

Additional endpoints such as subject satisfaction and preservation of subject comfort and anxiolysis were incorporated to support evidence of sedative/anxiolysis efficacy. The Aldrete score is a validated measure for discharge of patients from the PACU (Aldrete JA. The Post-Anesthesia Recovery Score Revisited. Journal of Clinical Anesthesia 1995;7:89-91). The ISAS is a reliable and validated tool to measure patient satisfaction with monitored anesthesia care (Dexter F, Aker J, Wright J. Development of a measure of patient satisfaction with monitored anesthesia care. Anesthesiology 1997;87:865-873).

Anaesthetist Assessment

Immediately after the subject was transferred to the PACU, the anaesthetist rated the ease of maintenance of appropriate intraoperative sedation level, respiratory stability, hemodynamic stability and subject cooperation using an anaesthetist assessment questionnaire.

Subject Pain Assessment

During the Double-Blind Treatment Period, the investigator or designee continually evaluated the study subject for the presence of pain. If rescue fentanyl was administered, the reason was documented. While in the PACU, the subject was asked to rate his/her pain level on a scale of 0-10 (where 0 is no pain and 10 is the worst pain ever experienced) every 15 minutes.

Aldrete Scoring System

The Aldrete Scoring System was administered upon arrival in the PACU and every 15 minutes thereafter while the subject remained in the PACU. Table 9 lists the criteria for the Aldrete Scoring System.

Table 9 Aldrete Scoring System

Activity		Score
Able to move voluntarily or on command	4 extremities = 2 extremities = 0 extremities =	2 1 0
Respiration	Able to deep breath and cough freely = Dyspnea, shallow or limited breathing = Apneic =	2 1 0
Circulation*	BP ± 20% of pre-sedation level = BP ± 21 to 49% of pre-sedation level = BP ± 50% of pre-sedation level =	2 1 0
Consciousness	Fully awake = Arousable on calling = Not responding =	2 1 0
O_2 Saturation	Able to maintain O_2 saturation >92% on room air = Needs O_2 inhalation to maintain O_2 saturation >90% = O_2 saturation <90% even with O_2 supplement =	2 1 0
TOTAL SCORE		

* The referenced Aldrete Scoring System contains an overlap in the scoring criteria for BP evaluation To avoid confusion in this study, the score of 1 was assigned a range of 21-49% instead of 20-49%.

Measure of Satisfaction with Anaesthesia and Anxiety

At the end of the Post-Treatment Period, subjects were visited or contacted by telephone for follow-up safety. Subjects also were evaluated for satisfaction with the anaesthetic procedure using the ISAS and level of anxiety before, during and after the study drug infusion process using the Anxiety Assessment Scale.

Randomisation

Subjects were assigned to receive DEX 0.5 mg/kg, DEX 1 mg/kg or PBO in a 2:2:1 ratio using a computer-generated randomization schedule. Randomisation was stratified by surgery/procedure type with the following strata: orthopaedic, ophthalmic, plastic vascular stents, breast, biopsies, AV fistulas, excision of lesions, protocol exemptions. Randomisation was implemented through IVRS.

Blinding

This was a double-blind study. All study personnel at the site, except the site pharmacist, were blinded to study drug assignment. The pharmacist received the bulk study drug and stored the supplies in a secure location. The pharmacist obtained the randomization assignment from the IVRS after a new subject had been identified and a medication order had been written.

The pharmacist prepared the IVRS-assigned study drugs in identical containers. Labeling attached to each container identified each bag for the period in which it is to be used (i.e., loading dose period and maintenance infusion period) along with the subject's unique identification number and initials.

The unblinding of study subjects during a clinical trial was not allowed unless there was a compelling medical or safety reasons to break the blinded treatment code [e.g., knowledge of the blinded information was necessary for treatment of serious adverse events (SAEs)]. The unblinded pharmacist was responsible for the security of the blinded randomization codes for the study. If it became necessary to break the blind, the

Principal Investigator (PI) contacted the unblinded pharmacist to obtain the specific treatment assignment for the subject in question. The sponsor was to be notified as soon as possible first by phone, then fax, regarding the necessity of breaking the blinded code. The PI notified the IRB, as required. Also, the date, time the blind was broken, and the reason for breaking the blind was documented on the subject's CRF.

Sample size

The primary efficacy analysis is to assess the sedative effect of DEX 1 mcg/kg load versus placebo in terms of percent of subjects not requiring MDZ for rescue sedation based on OAA/S score <=4. Sample size calculation was based on the following assumptions: percentage of subjects not requiring rescue sedation of more than 70% in the DEX 1 mcg/kg load group and less than 10% in the placebo group, 99% power, and normal approximation.

Statistical methods

Primary analysis

Efficacy analysis was performed on both the ITT and PP populations. The ITT population was the primary analysis population.

The primary efficacy analysis is to assess the sedative effect of DEX 1 mcg/kg load versus placebo in terms of percent of subjects not requiring MDZ for rescue sedation based on OAA/S score <=4. Statistical assessment comparing DEX 1 load versus Placebo and DEX 0.5 load versus Placebo was performed separately using Cochran-Mantel-Haenszel (CMH) test adjusting for surgery/procedure type (collapsed into 4 categories). Comparison of DEX 0.5 versus Placebo was tested in hierarchical manner.

Analytical strategy

The answer (yes/no) from the question "Has the subject required any rescue midazolam?" was used to derive the primary endpoint. Statistical assessments of the primary outcome comparing the DEX 1 mcg/kg load group versus PBO and the DEX 0.5 mcg/kg load group versus PBO were performed separately using the Cochran-Mantel-Haenszel (CMH) test controlled by surgery/procedure type. The comparison of DEX 1 mcg/kg load group versus PBO was the primary analysis (excluding DEX 0.5 mcg/kg load group). The efficacy claim was based only on the comparison of the DEX 1 mcg/kg load

group versus PBO. When comparing the DEX 0.5 mcg/kg load group versus PBO, the DEX 1 mcg/kg load group was excluded from analysis.

In order to control the probability of error in view of the two pairwise comparisons, the efficacy claim will only be based on the comparison of DEX 1 mcg/kg load group versus placebo. If this comparison fails to show statistically significant results in favor of DEX, no further statistical tests will be interpreted for this endpoint; all other p-values will be presented as planned and considered for explanatory purpose only. By this pre-specified procedure, no penalty in p-value is needed to control the probability of error.

Missing data

If a baseline value was missing, the value obtained during the screening period was used as the baseline value. Otherwise, there was no imputation of missing data.

Centre effects

This study included 26 investigational sites. No site enrolled more than 13% of all subjects. There were no adjustments made for centre in any of the analyses.

Subgroup analyses

Subgroup analyses were performed for each surgery/procedure type using a chi-square test. Testing of subgroups was exploratory.

Secondary analyses

The following analyses were performed:

Continuous secondary outcomes: ANOVA model adjusting surgery/procedure type

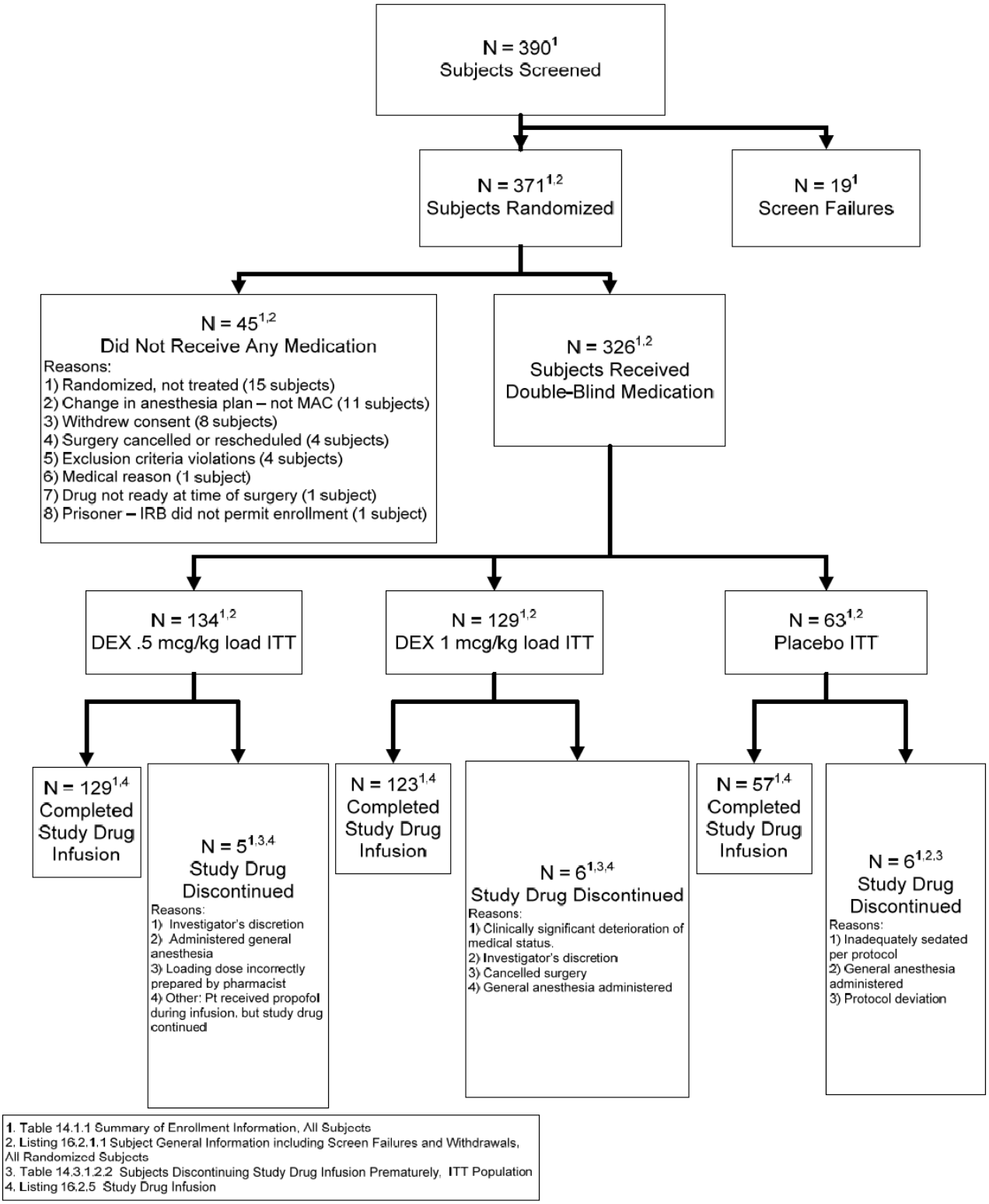
Time to event outcomes: Kaplan-Meir method and log-rank test adjusted for surgery/procedure type

Binary outcomes: Cochran-Mantel-Haenszel (CHM) adjusting for surgery/procedure type

Results

Participant flow

Figure 2 Disposition of Subjects



A total of 371 subjects who met the eligibility criteria were randomized to receive study drug, with 149 in the DEX 0.5 mcg/kg group, 149 in the DEX 1 mcg/kg group, and 73 in the PBO group. Of the randomized subjects, 134 (89.9%) in the DEX 0.5 mcg/kg group, 129 (86.6%) in the DEX 1 mcg/kg

group, and 63 (86.3) in the PBO group received study drug and were included in the safety/ITT analysis population. The ITT population included all subjects who received any amount of the randomized study drug and had at least one post-baseline efficacy measure. Subjects were terminated during the post-treatment period mainly due to being lost to follow-up or withdrawing consent. One subject (who received placebo) was terminated due to an adverse event and 3 subjects (2 received DEX 1 mcg/kg and 1 received placebo) were terminated due to protocol violations. Protocol violations are described in Section 10 of the CSR.

The PP analysis population excluded 33 (22.1%) subjects in the DEX 0.5 mcg/kg group, 34 (22.8%) in the DEX 1 mcg/kg group and 25 (34.2%) in the PBO group. The most common reason that subjects qualifying to be in the ITT population were excluded from the PP population was that study drug was not titrated before the subject was given rescue MDZ. Subjects excluded from the ITT and PP populations are listed, along with the reason for exclusion, in Appendices 16.2.3.1 and 16.2.3.2 of the CSR.

Table 10 All Randomized Subjects

Study Subjects	Number (%) of Subjects			
	DEX 0.5 mcg/kg n (%)	DEX 1 mcg/kg n (%)	PBO n (%)	Total n (%)
All Randomized Subjects	149	149	73	371
Safety/Intent to-Treat Population	134 (89.9)	129 (86.6)	63 (86.3)	326 (87.9)
Per Protocol Population	116 (77.9)	115 (77.2)	48 (65.8)	279 (75.2)
Study Terminations	20 (13.4)	24 (16.1)	11 (15.1)	55 (14.9)
Reasons for Study Termination				
Adverse Event	0	0	1 (1.4)	1 (0.3)
Lost to Follow-up	5 (3.4)	4 (2.7)	0	9 (2.4)
Withdrew Consent	3 (2.0)	4 (2.7)	1 (1.4)	8 (2.2)
Protocol Violation	0	2 (1.3)	1 (1.4)	3 (0.8)
Other	12 (8.1)	14 (9.4)	8 (11.0)	34 (9.2)

134 (89.9%) of the 149 subjects randomized to receive DEX 0.5 mcg/kg, 129 (86.6%) of the 149 subjects randomized to receive DEX 1 mcg/kg group, and 63 (86.3%) of the 73 subjects randomized to receive PBO received study drug infusion. Study drug was discontinued prematurely in 17 subjects: 5 (3.4%) subjects in the DEX 0.5 mcg/kg group, 6 (4.0%) subjects in DEX 1 mcg/kg group and 6 (8.2%) subjects in PBO group.

In the DEX 0.5 mcg/kg group subject 211-0019 had study drug discontinued because of a pharmacy error in preparing the loading dose. Subject 209-0002 had study drug stopped after infusing for 17 minutes because of urticaria at the IV site. Subject 201-0030 had study drug discontinued at the same time as surgery was completed and was therefore not an early discontinuation *per se.* Subjects 206-0003 and 222-0002 had study drug stopped due to inadequate sedation and received general anesthesia.

In the DEX 1.0 mcg/kg group, subjects 202-0001 and 206-0011 were discontinued because their surgery was cancelled. Subject 211-0021 was converted to general anesthesia at the request of the surgeon. Subject 214-0002 had study drug discontinued due to hypotension. Subject 223-0011 was discontinued for bradycardia. Subject 226-0047 had study drug discontinued because she was "too sleepy."

In the placebo group 6 subjects had study drug discontinued. Three subjects (201-0013, 211-0014 and 218-0005) were unable to be adequately sedated by protocol-allowed amounts of study drug and rescue medication. Three subjects were cancelled for other reasons: two (206-0001 and 206-0014) because of a partially successful block and one (217-0011) who received additional rescue medication for pain.

Table 11 Disposition: All Subjects

Study Subjects	Number (%) of Subjects			
	DEX 0.5 mcg/kg N=149 n (%)	DEX 1 mcg/kg N=149 n (%)	PBO N=73 n (%)	Total N=371 n (%)
Subjects Screened	–	–	–	390
Screen Failures	–	–	–	19
Subjects Randomized	149 (100.0)	149 (100.0)	73 (100.0)	371 (100.0)
Randomized, not Treated	15 (10.1)	20 (13.4)	10 (13.7)	45 (12.1)
Received Study Drug Infusion	134 (89.9)	129 (86.6)	63 (86.3)	326 (87.8)
Study Drug Infusion Completed	129 (86.6)	123 (82.6)	57 (78.1)	309 (83.3)
Study Drug Infusion Stopped	5 (3.4)	6 (4.0)	6 (8.2)	17 (4.6)
Completed Post Treatment Period	128 (85.9)	125 (83.9)	62 (84.9)	315 (84.9)
Did Not Complete Post Treatment	21 (14.1)	24 (16.1)	11 (15.1)	56 (15.1)
Completed Both Periods	125 (83.9)	118 (79.2)	57 (78.1)	300 (80.9)

Conduct of the study

Protocol deviations are listed in Appendix 16.2.2 of the CSR and included the following:

- inclusion/exclusion criteria not met,
- pharmacy error
- study drug not titrated before MDZ administration, and
- MDZ being given outside the time allowed per the protocol

One subject (209-0008) who received PBO did not meet the inclusion/exclusion criteria due to use of clonidine (α-2 agonist) and excluded from the PP population.

One subject (235-0015) who received DEX 0.5 mcg/kg had the Screening assessment one day outside of the prescribed window, but as this was a minor violation the subject was included in the PP population.

For two subjects at one site (237-0006 who received DEX 0.5 mcg/kg and 237-0018 who received PBO) there were pharmacy errors in preparing the study drug. Neither subject had an adverse event as a result and at no time was safety an issue. These subjects were excluded from the PP population.

Three subjects (202-0008 who received DEX 1 mcg/kg; 202-0007 and 205-0008 who received PBO) had MDZ administered outside the time allowed by the protocol. They were excluded from the PP population.

Fourteen subjects were granted waivers by the sponsor for minor study entry criteria violations prior to study admission (Listing 16.2.4.12). Eleven subjects (5 who received DEX 0.5 mcg/kg, 4 who received DEX 1 mcg/kg and 2 who received PBO) had a procedure different from the categories described in the protocol; mostly for inguinal hernia repair. One subject (223-0011), who received DEX 1 mcg/kg, received a waiver for baseline heart rate < 50, 1 subject (206-0016) who received PBO, was entered with a waiver for the use of topical lidocaine for eye surgery and 1 subject who received PBO (235-0015) was one day out of the screening window. Appendix 16.2.4.12 does not indicate a waiver for subject 235-0015 however this subject was granted a waiver for being one day out of the screening window prior to study drug infusion (See CRF for subject 235-0015). These subjects were included in the PP population.

For 41 subjects, study drug was not titrated up prior to administering rescue MDZ. This included 17 subjects who received DEX 0.5 mcg/kg, 13 who received DEX 1 mcg/kg, and 11 who received PBO. These subjects were not included in the PP population. These protocol deviations had no effect on the study endpoints. All other deviations were minor and did not affect study drug efficacy or safety evaluations or subject safety.

Baseline data

A summary of demographic and key baseline characteristic information for the all patients treated population is presented below.

Table 12 Demographics by Treatment Group (Safety Population)

Variable	DEX 0.5 mcg/kg N=134	DEX 1 mcg/kg N=129	PBO N=63	p-value
Age (Years)	–	–	–	p ≥ 0.541
Mean (SD)	56.8 (16.51)	53.8 (16.47)	55.3 (16.69)	–
Range	18 – 93	19 – 88	20 – 80	–
Gender [n (%)]	–	–	–	p ≥ 0.379
Male	68 (50.7)	65 (50.4)	36 (57.1)	–
Female	66 (49.3)	64 (49.6)	27 (42.9)	–
Ethnic Origin [n (%)]	–	–	–	p ≥ 0.807
Caucasian	91 (67.9)	74 (57.4)	39 (61.9)	–
Black	23 (17.2)	30 (23.3)	14 (22.2)	–
Asian	1 (0.7)	3 (2.3)	1 (1.6)	–
Hispanic	18 (13.4)	22 (17.1)	9 (14.3)	–
Other	1 (0.7)	0	0	–
Weight (kg)	–	–	–	p ≥ 0.212
Mean (SD)	84.9 (21.02)	83.0 (19.34)	86.9 (21.75)	–
Range	51 – 167	45 – 155	48 – 136	–

Primary analysis of efficacy (ITT population)

The results for the primary efficacy endpoint the percent of subjects not requiring MDZ for rescue sedation based on achieving and/or maintaining an OAA/S ≤4 throughout the study drug infusion period, are summarized by treatment group in the following table.

Table 15 Number (%) of Subjects Not Requiring Rescue Midazolam (ITT Population)

Rescue MDZ/ No Rescue MDZ	DEX 0.5 mcg/kg N=134 n (%)	DEX 1 mcg/kg N=129 n (%)	PBO N=63 n (%)
Did Not Require Rescue MDZ	54 (40.3)	70 (54.3)	2 (3.2)
Required Rescue MDZ[a]	80 (59.7)	59 (45.7)	61 (96.8)
p-value[b]	< 0.001	< 0.001	–

a Rescue MDZ was given in 0.5 mg increments IV as needed to maintain OAA/S ≤ 4.

b p-value based on CMH test, adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

The two patients in the placebo group who did not require rescue MDZ both had ophthalmic procedures.

Table 16 Number (%) of Subjects Not Requiring Rescue Midazolam by Surgery/Procedure Type (ITT Population)

MDZ Usage[a]	DEX 0.5 mcg/kg N=134 n (%)	p – value[b]	DEX 1 mcg/kg N=129 n (%)	p - value[b]	PBO N=63 n (%)
Pooled Type 1 (Orthopedic)					
n	38	–	39	–	20
MDZ not required	15 (39.5)	0.001	22 (56.4)	< 0.001	0
MDZ required	23 (60.5)	–	17 (43.6)	–	20 (100.0)
Pooled Type 2 (Ophthalmic)					
n	34	–	35	–	18
MDZ not required	19 (55.9)	0.002	25 (71.4)	< 0.001	2 (11.1)
MDZ required	15 (44.1)	–	10 (28.6)	–	16 (88.9)
Pooled Type 3 (Breast Biopsies, Excision of Lesions and Plastic)					
n	38	–	34	–	15
MDZ not required	8 (21.1)	0.054	11 (32.4)	0.012	0
MDZ required	30 (78.9)	–	23 (67.6)	–	15 (100.0)
Pooled Type 4 (AV Fistulas, Vascular Stents and Other)					
n	24	–	21	–	10
MDZ not required	12 (50.0)	0.005	12 (57.1)	0.002	0
MDZ required	12 (50.0)	–	9 (42.9)	–	10 (100.0)

a Subjects not requiring rescue MDZ sedation based on achieving/ maintaining an OAA/S score ≤ 4 throughout study drug infusion.

b p-values based on Pearson Chi-square test comparing each DEX arm versus the placebo arm.

Secondary analyses

As the primary analysis is spectacularly uninformative about the key question of scientific interest, the main information concerning the usefulness of Dexdor in the clinical situation studied will come from the secondary analyses. As the trial design does not allow for a direct comparison of the DEX regimens against standard of care sedation with midazolam (+/- fentanyl) and there is inherent bias in DEX vs. MDX comparisons, interpretation of the secondary analyses must be extremely cautious. The results for the key secondary analyses pre-specified in the protocol are presented in the following tables.

Table 17 Total Dose of Rescue Midazolam (ITT Population)

Total dose of MDZ rescue medication (mg)[a]	DEX 0.5 mcg/kg N=134	DEX 1 mcg/kg N=129	PBO N=63
Mean (SD)	1.4 (1.69)	0.9 (1.51)	4.1 (3.02)
Median	1.0	0.0	3.5
Range	0.0 – 8.0	0.0 – 7.0	0.0 – 14.0
p-value[b]	< 0.001	< 0.001	-

a Rescue MDZ was given in 0.5 mg increments IV as needed to maintain OAA/S ≤ 4.

b p-values based on one-way ANOVA adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Table 18 Total Dose of Rescue Midazolam by Surgery/Procedure Type (ITT Population)

Total dose of MDZ rescue medication (mg)[a]	DEX 0.5 mcg/kg N=134 n (%)	DEX 1 mcg/kg N=129 n (%)	PBO N=63 n (%)
Pooled Type 1 (Orthopedic)			
n	38	39	20
Mean (SD)	1.9 (2.40)	1.0 (1.73)	5.6 (3.65)
Median	1.0	0.0	4.3
Range	0.0 – 8.0	0.0 – 7.0	1.0 – 14.0
p-value	< 0.001	< 0.001	-
Pooled Type 2 (Ophthalmic)			
n	34	35	18
Mean (SD)	0.7 (1.17)	0.4 (0.71)	2.1 (1.73)
Median	0.0	0.0	1.8
Range	0.0 – 5.0	0.0 – 3.0	0.0 – 6.0
p-value	0.001	< 0.001	-
Pooled Type 3 (Breast Biopsies, Excision of Lesions and Plastic)			
n	38	34	15
Mean (SD)	1.7 (1.27)	1.5 (1.68)	4.3 (2.36)
Median	2.0	1.0	4.0
Range	0.0 – 4.0	0.0 – 7.0	1.5 – 9.0
p-value	< 0.001	< 0.001	-
Pooled Type 4 (AV Fistulas, Vascular Stents and Other)			
n	24	21	10
Mean (SD)	0.9 (1.12)	1.0 (1.54)	4.2 (2.69)
Median	0.3	0.0	3.8
Range	0.0 – 3.0	0.0 – 6.0	1.0 – 9.0
p-value	< 0.001	< 0.001	-

a Rescue MDZ was given in 0.5 mg increments IV as needed to maintain OAA/S ≤ 4.

Table 19 Total Dose of Rescue Midazolam Considering Only Subjects Who Received Rescue Midazolam (ITT Population)

Total dose of MDZ rescue medication (mg)[a]	DEX 0.5 mcg/kg N=134	DEX 1 mcg/kg N=129	PBO N=63
n	80	59	61
Mean (SD)	2.3 (1.64)	2.1 (1.65)	4.2 (2.97)
Median	2.0	1.5	4.0
Range	0.5 – 8.0	0.5 – 7.0	0.5 – 14.0
p-value[b]	< 0.001	< 0.001	-

a Rescue MDZ was given in 0.5 mg increments IV as needed to maintain OAA/S ≤ 4.

b p-values based on one-way ANOVA adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Table 20 Time to Receiving First Dose of Rescue Midazolam (ITT Population)

Time to first dose of MDZ rescue medication[a]	DEX 0.5 mcg/kg N=134	DEX 1 mcg/kg N=129	PBO N=63
Number in analysis	134	128	63
Number of events	80	58	61
Median time (minutes)	40.0	114.0	20.0
95% Confidence Limits (minutes)	21.0, 77.0	64.0, –[c]	17.0, 24.0
p-value[b]	< 0.001	< 0.001	–

a Rescue MDZ was given in 0.5 mg increments IV as needed to maintain OAA/S ≤ 4.

b p-values based on log-rank test adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

c Upper limit of the confidence interval could not be calculated because less than 50% of the subjects received rescue MDZ.

Table 21 Kaplan-Meier Analysis of Time to Recovery and Readiness for Discharge from PACU (ITT Population)

Time to Recovery and Readiness for Discharge from PACU[a]	DEX 0.5 mcg/kg N=134	DEX 1 mcg/kg N=129	PBO N=63
Number in analysis	133	127	62
Number of events	132	127	62
Median time (minutes)	29.0	25.0	14.0
95% Confidence Limits (minutes)	21.0, 41.0	20.0, 35.0	10.0, 20.0
p-value[b]	0.068	0.076	–

a Time from discontinuation of study drug to reaching Aldrete score ≥ 9 and satisfying PACU criteria for discharge.

b p-values based on log-rank test adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Table 22 Number (%) of Subjects Requiring Rescue Fentanyl (ITT Population)

Time Period	DEX 0.5 mcg/kg N=134 n (%)	p – value[a]	DEX 1 mcg/kg N=129 n (%)	p – value[a]	PBO N=63 n (%)
Infusion Period					
Required Fentanyl	79 (59.0)	< 0.001	55 (42.6)	< 0.001	56 (88.9)
Did Not Require Fentanyl	55 (41.0)	–	74 (57.4)	–	7 (11.1)
PACU Period					
Required Fentanyl	5 (3.7)	0.104	5 (3.9)	0.105	6 (9.5)
Did Not Require Fentanyl	129 (96.3)	–	124 (96.1)	–	57 (90.5)
Overall					
Required Fentanyl	81 (60.4)	< 0.001	56 (43.4)	< 0.001	56 (88.9)
Did Not Require Fentanyl	53 (39.6)	–	73 (56.6)	–	7 (11.1)

a p-value based on CMH test, adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

The percentage of subjects who required rescue fentanyl during the infusion period was significantly lower for both of the DEX groups (59.0% of subjects randomized to receive DEX 0.5 mcg/kg and 42.6% of subjects randomized to receive DEX 1 mcg/kg) compared to 88.9% for the PBO group

Table 23 Total Dose of Rescue Fentanyl (ITT Population)

Total Dose of Fentanyl Rescue Medication (mcg)	DEX 0.5 mcg/kg N=134	DEX 1 mcg/kg N=129	PBO N=63
Infusion Period (n)	79	55	56
Mean (SD)	84.8 (52.94)	83.6 (52.75)	144.4 (100.15)
Median	75.0	75.0	100.0
Range	10.0 – 275.0	25.0 – 300.0	12.0 – 500.0
p-value[a]	< 0.001	< 0.001	–
PACU Period (n)	5	5	6
Mean (SD)	35.0 (13.69)	45.0 (27.39)	58.3 (34.16)
Median	25.0	25.0	50.0
Range	25.0 – 50.0	25.0 – 75.0	25.0 – 100.0
p-value[a]	0.138	0.269	–
Overall (n)	81	56	56
Mean (SD)	84.9 (54.22)	86.2 (55.99)	150.7 (100.31)
Median	75.0	75.0	100.0
Range	10.0 – 275.0	25.0 – 300.0	12.0 – 500.0
p-value[a]	< 0.001	< 0.001	–

a p-value from ANOVA model adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

A significantly larger dose of fentanyl was required for the PBO group during the infusion period (144.4 mcg as compared with 84.8 and 83.6 mcg for the DEX 0.5 and 1 mcg treatment groups, respectively) and overall (150.7 mcg as compared with 84.9 and 86.2 mcg for the DEX 0.5 and 1 mcg treatment groups, respectively). No significant differences were observed during the PACU period.

Table 24 Subjects Requiring Additional Medication for Pain (ITT Population)

Time Period	DEX 0.5 mcg/kg N=134 n (%)	p – value[a]	DEX 1 mcg/kg N=129 n (%)	p – value[a]	PBO N=63 n (%)
Infusion Period					
Required Additional Pain Medication[b]	2 (1.5)	0.466	0	0.048	2 (3.2)
Did Not Require Additional Pain Medication	132 (98.5)	–	129 (100.0)	–	61 (96.8)
PACU Period					
Required Additional Pain Medication[b]	21 (15.7)	0.680	9 (7.0)	0.025	11 (17.5)
Did Not Require Additional Pain Medication	113 (84.3)	–	119 (92.2)	–	52 (82.5)
Overall					
Required Additional Pain Medication[b]	23 (17.2)	0.509	9 (7.0)	0.005	13 (20.6)
Did Not Require Additional Pain Medication	111 (82.8)	–	120 (93.0)	–	50 (79.4)

a p-value based on CMH test, adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

b Additional medications included hydromorphone hydrochloride, morphine, oxycocet, oxycodone, paracetamol, pethidine hydrochloride, vicodin, alfentanil, bupivacaine hydrochloride, lidocaine, propofol, ketorolac and ketorolac tromethamine.

For all comparisons (infusion period, PACU period and overall) between the DEX 1 mcg/kg group and the PBO group, the differences were significant ($p \leq 0.048$) with more subjects in the PBO group requiring pain medication in addition to fentanyl.

Differences between the DEX 0.5 mcg/kg group and the PBO group were not significant at any time period. Postoperatively, during the PACU period, as the local anaesthetic blocks wore off, significantly fewer subjects in the DEX 1 mcg/kg group required analgesics than in the PBO group.

Table 25 Anesthesiologists' Assessment Using Visual Analog Scale (ITT Population)

Anesthesiologist Assessment[a]	DEX 0.5 mcg/kg N=134 Mean (SD)	p – value[b]	DEX 1 mcg/kg N=129 Mean (SD)	p – value[b]	PBO N=62[c] Mean (SD)
Ease of Maintenance of Sedation Level (cm)	2.8 (2.68)	< 0.001	2.2 (2.23)	< 0.001	4.4 (2.95)
Hemodynamic Stability (cm)	2.5 (2.39)	0.085	2.3 (2.27)	0.342	2.0 (2.08)
Respiratory Stability (cm)	1.4 (1.57)	0.208	1.7 (2.01)	0.650	1.8 (2.04)
Subject Cooperation (cm)	1.9 (2.04)	0.642	1.9 (2.18)	0.757	2.0 (2.23)

a The Anesthesiologist assessment was performed using Visual Analog Scale (VAS) scores (cm). The VAS scores ranged from 0 to 10, with the most favorable outcome associated with the lowest score.

b p-values from ANOVA model adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

c One subject excluded from VAS analysis

Table 26 Overall Subject Assessment of Satisfaction (ITT Population)

Subject Assessment[a]	DEX 0.5 mcg/kg N=134 Mean (SD)	p – value[b]	DEX 1 mcg/kg N=129 Mean (SD)	p – value[b]	PBO N=63 Mean (SD)
1 - I threw up or felt like throwing up	2.2 (1.67)	0.959	2.2 (1.70)	0.970	2.2 (1.74)
2 - I would have the same anesthetic again	2.2 (1.32)	<0.001	1.8 (2.02)	0.054	1.2 (2.35)
3 - I itched	2.4 (1.26)	0.064	2.4 (1.34)	0.051	2.0 (1.76)
4 - I felt relaxed	1.8 (1.71)	0.009	1.9 (1.64)	0.002	1.0 (2.44)
5 - I felt pain	1.6 (1.98)	< 0.001	1.3 (2.16)	0.002	0.3 (2.28)
6 - I felt safe	2.1 (1.40)	0.409	2.3 (1.33)	0.092	1.9 (1.68)
7 - I was too hot or cold	1.9 (1.79)	0.792	2.1 (1.69)	0.264	1.8 (1.83)
8 - I was satisfied with the anesthesia care	2.5 (1.06)	0.007	2.6 (0.90)	<0.001	1.9 (1.82)
9 - I felt pain during surgery	1.3 (2.11)	0.159	1.8 (1.91)	0.006	0.9 (2.33)
10 - I felt good	1.7 (1.72)	0.075	1.8 (1.66)	0.019	1.2 (2.17)
11 - I hurt	1.8 (1.89)	0.002	1.9 (1.83)	<0.001	0.8 (2.36)
Overall ISAS Score	2.0 (0.97)	<0.001	2.0 (0.97)	<0.001	1.4 (1.39)

a Subject assessment from (ISAS). For items 1, 3, 5, 7, 9, and 11, the scores are re-assigned as: +3=disagree very much; +2= disagree moderately; +1= disagree slightly; -1= agree slightly; -2= agree moderately; -3=agree very much. For items 2, 4, 6, 8 and 10 the scores are re-assigned as: -3=disagree very much; -2=disagree moderately; -1=disagree slightly; +1=agree slightly; +2=agree moderately; +3=agree very much. The Overall ISAS Score is the mean of all re-assigned item scores. The higher score indicates more favorable outcome.

b p-values from ANOVA model adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Table 27 Overall Subject Assessment of Anxiety (ITT Population)

Anxiety Assessment[a]	DEX 0.5 mcg/kg N=134 Mean (SD)	p – value[b]	DEX 1 mcg/kg N=129 Mean (SD)	p – value[b]	PBO N=63 Mean (SD)
Before Surgery (n)	128	0.125	124	0.708	63
Mean (SD)	3.2 (2.75)	–	3.7 (2.82)	–	3.9 (2.86)
Median	3.0	–	4.0	–	4.0
Range	0.0 – 10.0	–	0.0 – 10.0	–	0.0 – 10.0
During Surgery (n)	128	0.188	123	0.208	62
Mean (SD)	1.6 (2.35)	–	1.6 (2.60)	–	2.1 (2.64)
Median	0.0	–	0.0	–	1.0
Range	0.0 – 9.0	–	0.0 – 10.0	–	0.0 – 9.0
After Surgery (n)	128	0.068	123	0.007	62
Mean (SD)	1.3 (2.26)	–	1.0 (1.88)	–	1.9 (2.72)
Median	0.0	–	0.0	–	0.0
Range	0.0 – 10.0	–	0.0 – 10.0	–	0.0 – 9.0

a Subject assessment from Anxiety Assessment Scale where scores range from 0 (no anxiety) to 10 (extreme anxiety).

b p-values from ANOVA model adjusting for surgery/procedure type comparing each DEX arm versus the placebo arm.

Efficacy conclusions for MAC trial (2005-005)

The CSR for the MAC trial (2005-005) provides the following discussion on efficacy.

Efficacy results showed that DEX was more effective than PBO when used to sedate non-intubated subjects requiring MAC during surgical and diagnostic procedures. The primary efficacy result showed that both doses of DEX were significantly better than PBO at maintaining the targeted sedation level of OAA/S < 4 without the use of additional MDZ. In this study, 54.3% (70/129) of subjects randomized to receive DEX 1 mcg/kg and 40.3% (54/134) of subjects randomized to receive DEX 0.5 mcg/kg did not require rescue MDZ compared to 3.2% (2/63) for the PBO group ($p < 0.001$ for both comparisons). More subjects in PBO group could not be sedated with protocol-specified amounts of study drug or rescue MDZ and required additional sedation (propofol) or general anesthesia to complete their surgical procedure. Efficacy was supported by the secondary endpoints:

(1) The mean total dose of rescue MDZ used to achieve and/or maintain the targeted sedation level was significantly lower in both DEX groups: 0.9 mg for DEX 1 mcg/kg and 1.4 mg for DEX 0.5 mcg/kg, compared to 4.1 mg for the PBO group.

(2) The median time from start of study drug to first dose of rescue MDZ was significantly longer in both DEX groups: 114 minutes for DEX 1 mcg/kg and 40 minutes for DEX 0.5 mcg/kg compared to 20 minutes for PBO ($p < 0.001$ for each comparison).

(3) Fewer subjects in each DEX group required alternate sedation and/or general anesthesia: 2 (1.6%) DEX 1 mcg/kg subjects and 4 (3.0%) DEX 0.5 mcg/kg subjects compared to 7 (11.1%) PBO subjects.

(4) The percentage of subjects who required rescue fentanyl for analgesia during the infusion period was significantly lower for both DEX groups (42.6% of DEX 1 mcg/kg subjects and 59.0% of DEX 0.5 mcg/kg subjects compared to 88.9% of PBO subjects ($p < 0.001$ for both comparisons); and the dose of fentanyl during study drug infusion was significantly lower in both DEX groups, 83.6 and 84.8 mcg

of fentanyl for DEX 1 and 0.5 mcg/kg, respectively, compared to 144.4 mcg of fentanyl in the PBO group ($p < 0.001$ for each comparison).

(5) Significantly fewer subjects required postoperative analgesics in the DEX 1 mcg/kg group than in the PBO group ($p = 0.025$).

(6) The anesthesiologists' assessment using the VAS showed significantly easier maintenance of the targeted sedation level in each DEX group compared to PBO group ($p < 0.001$ for each comparison). There was no difference between groups for anesthesiologists' assessment of subject cooperation.

(7) Overall, subjects ISAS scores were significantly higher in each DEX group compared to the PBO group ($p< 0.001$ for each comparison). Postoperative subject anxiety was significantly lower in the DEX 1 mcg/kg group than PBO.

Main study AWAKE (2005-006)

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Dexmedetomidine Used for Sedation During Elective Awake Fiberoptic Intubation

Methods

This was a Phase III, randomized, double blind, PBO-controlled, multicentre (17 sites) study designed to evaluate the safety and efficacy of DEX (1 mcg/kg loading dose with 0.7 mcg/kg/hr maintenance dose) for sedation in subjects with potentially difficult airways undergoing awake fibreoptic intubation prior to an elective surgical or diagnostic procedure.

Following screening eligible subjects were randomized to receive either DEX or PBO in a 1:1 ratio through an IVRS using a computer generated randomization schedule. At baseline, subjects' blood pressure (BP), respiratory rate (RR), heart rate (HR) and oxygen saturation by pulse oximetry (SpO2) were measured. A 12-lead ECG was performed and a Ramsay Sedation Scale (RSS) score was documented. Blood samples for safety analyses were collected and, for female subjects of childbearing potential, a urine pregnancy test was performed.

After completion of baseline procedures, each subject was pre-medicated with glycopyrrolate prior to study drug infusion. Supplemental oxygen by nasal cannula or facemask was started and continued throughout the study period. During study drug infusion, subjects in the DEX group received a DEX loading dose of 1 mcg/kg over 10 minutes followed immediately by a DEX maintenance infusion of 0.7 mcg/kg/hr. Subjects in the PBO group received a matching volume of normal saline for both the loading dose and maintenance infusion.

Five minutes after beginning maintenance infusion (i.e. 15 minutes after start of loading dose infusion), the RSS was repeated. Subjects scoring 1 on the RSS received rescue MDZ 0.5 mg doses as needed (PRN) up to a maximum 0.2 mg/kg until the RSS score was $\geq$ 2. RSS scores were obtained every 3 minutes from the 15 minute time point until the end of study drug infusion. Any subject scoring 1 on the RSS at any time received rescue MDZ, 0.5 mg doses, until the RSS was $\geq$ 2.

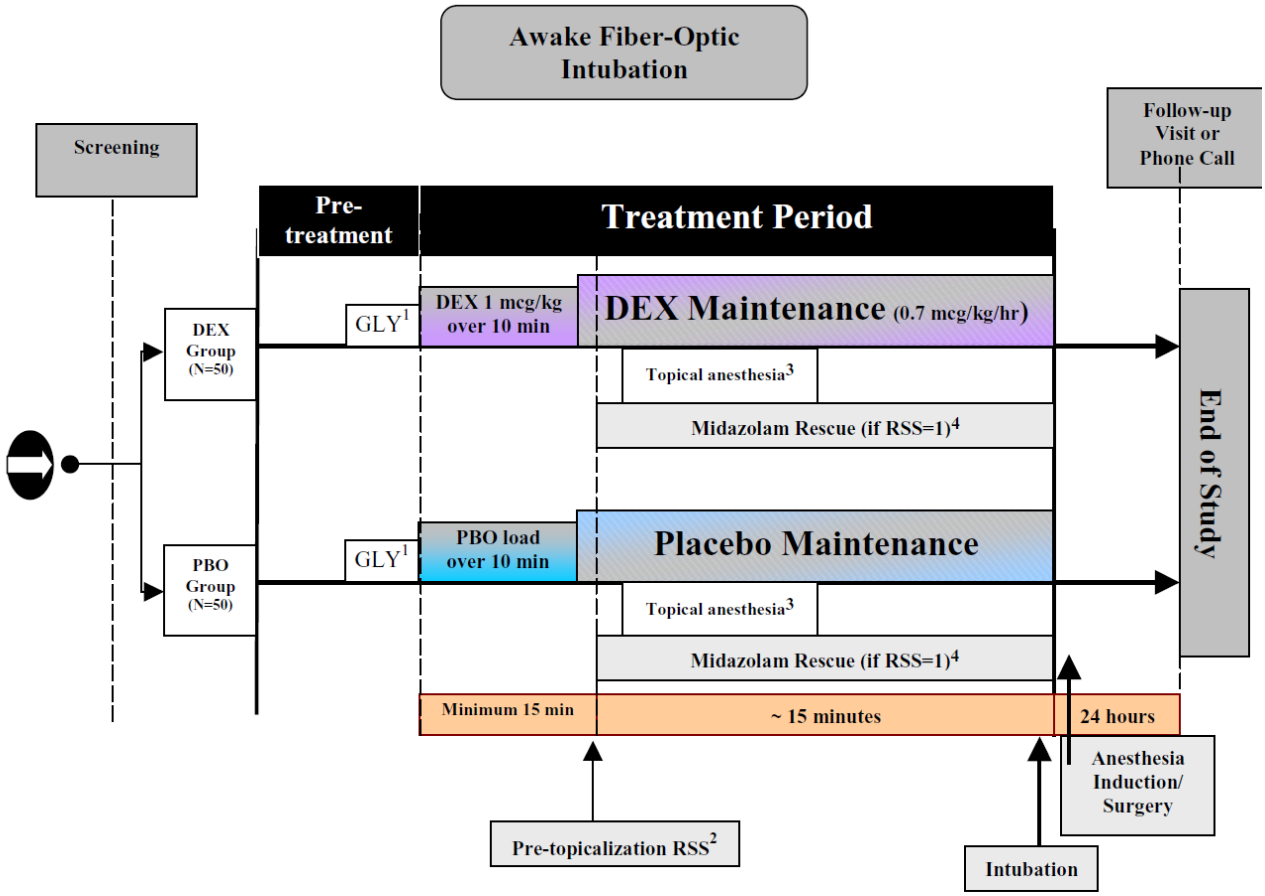
After achieving protocol-defined sedation and no sooner than 15 minutes after the start of study drug infusion, topical anesthesia in the nasopharynx, oropharynx, hypopharynx, and glottis was applied using lidocaine. After topicalization, an RSS score was obtained and any subject with a score of 1 received rescue MDZ until the RSS score was $\geq$ 2. After adequate topical anesthesia and achievement of an RSS score of $\geq$ 2, nasal or oral intubation using a flexible fibreoptic bronchoscope was

performed. During the fibreoptic procedure, MDZ PRN (maximum total dose of 0.2 mg/kg) was given as rescue for sedation in order to maintain the RSS score at ≥ 2. Subjects' RSS scores were recorded before receiving each dose of rescue medication.

Following completion of intubation, the subject's endotracheal tube was connected to the breathing circuit. A positive-pressure breath with a tidal volume of 5-7 mL/kg was administered and the end–tidal CO2 was recorded. Blood samples for safety analyses were collected. Study drug infusion was then discontinued, general anesthesia induced, and the scheduled surgery/procedure proceeded as planned.

Vital signs (BP, HR, RR, pulse oximetry) were recorded every 3 minutes from the start of study drug infusion until the completion of intubation and immediately after discontinuation of study drug. Continuous cardiac monitoring was performed throughout study drug administration and a 12-lead ECG was performed after study drug infusion was discontinued but prior to the scheduled surgery/procedure.

Immediately following intubation, anaesthetists responded to questions related to the intubation using Visual Analog Scales (VAS). Subjects began the 24-Hour Follow-Up Period at the time of study drug discontinuation. At the end of the 24-Hour Follow-Up Period, subjects were assessed for recall of intubation, discomfort and satisfaction. A schematic of the overall study design is provided below.



DEX = dexmedetomidine; PBO = Placebo.

1 GLY = glycopyrrolate 0.1 mg IV; nasal cannula or face mask oxygen.

2 RSS performed 15 minutes after start of study drug and before topicalization. MDZ, 0.5 mg IV, given for RSS score of 1.

3 Local anesthetic lidocaine. Topicalization did not begin until RSS ≥ 2. Topicalization assessed by absence of gag reflex.

4 MDZ, 0.5 mg increments IV as needed (maximum 0.2 mg/kg) for target RSS score of ≥2.

Study participants

Male or female subjects requiring sedation for awake fibreoptic (oral or nasal) intubation because of anticipated difficult airway, and meeting the inclusion and exclusion criteria below, were selected and screened for enrolment.

Key Inclusion Criteria

- Any age >18, any fitness for anaesthesia (ASA grade I to IV), no pregnancy possibility.

Key Exclusion Criteria

- Recent alpha-2-agonist, opioid within 1-4 hours, recent MI or unstable angina. Otherwise no restriction on prior and concomitant therapy.
- Specified CNS or psychiatric disease, abnormal liver function.

The Mallampati classification relates tongue size to pharyngeal size and is assigned based on the pharyngeal structures as follows:

Class I = visualization of the soft palate, fauces, uvula, anterior and posterior pillars.

Class II = visualization of the soft palate, fauces and uvula.

Class III = visualization of the soft palate and the base of the uvula.

Class IV = soft palate is not visible at all.

Subjects who were unable to open their mouths due to anatomical abnormalities were classified as Mallampati IV.

For the ASA Physical Status Classification System, subjects were classified as:

ASA I A normal healthy patient

ASA II A patient with mild systemic disease

ASA III A patient with severe systemic disease

ASA IV A patient with severe systemic disease that is a constant threat to life

ASA V A moribund patient who is not expected to survive without the operation

Treatments

Study drug was prepared (diluted) by the site pharmacy in an IV bag to a concentration of 4 mcg/mL. It was infused using a controlled infusion device such as a standard intravenous infusion pump system. Study drug was not rapidly bloused. Sedation dosages were calculated using the subject's most recently measured weight.

Each subject was pre-medicated with glycopyrrolate prior to study drug infusion. No sedating agents other than DEX or MDZ were permitted during the study treatment period, including opioids and topical cocaine and phenylephrine that might be used for nasal mucosa vasoconstriction.

Blinded study drug was administered as a two-stage infusion:

- a loading dose infusion of either DEX 1 mcg/kg administered over 10 minutes or matched PBO, at least 15 minutes prior to the start of topicalization procedures for the fibreoptic intubation
- a maintenance dose infusion of DEX 0.7 mcg/kg/hr or matched PBO continued through completion of intubation.

The loading dose and maintenance dose ranges for this study were within the dose ranges recommended in the SPC for DEX.

- The DEX package insert states that treatment is generally initiated with a loading dose of 1 mcg/kg given over 10 minutes. This protocol specified that the loading dose of DEX was 1 mcg/kg over 10 minutes.

- The maintenance dose range for DEX in this protocol was 0.7 mcg/kg/hr, which is also within the recommended maintenance dose range of 0.2 to 0.7 mcg/kg/hr listed in the package insert.

If the subject required sedation based on an RSS score of 1, rescue doses of MDZ, 0.5 mg IV boluses were given. This dose could be repeated to a maximum of 0.2 mg/kg to achieve and/or maintain a target RSS score of ≥ 2. If the subject remained inadequately sedated (RSS score = 1) with a total dose of 0.2 mg/kg of MDZ, at the anaesthetist's discretion other rescue medication could be given for subject comfort and/or safety. The administration (dosage, total dose, and time) of supplemental MDZ or other rescue medication was recorded on the appropriate CRF. If a subject required rescue medication other than MDZ, study drug was stopped and the subject was considered a treatment failure.

Topicalization

After achieving protocol-defined sedation (RSS score ≥2), topical anesthesia in the nasopharynx, oropharynx, hypopharynx, and glottis was achieved using lidocaine as described below. Topicalization was not to begin until 15 minutes or more after the start of study drug. The following procedure for airway topicalization was followed:

1. Nebulized 4% lidocaine (2 - 4 mL) was delivered over a 10-minute period using a standard nebulizer with oxygen 8 - 10 L/min as a driving gas.

2. If possible, the subject gargled with 4 % viscous lidocaine (1 - 2 mL).

3. If nasal intubation was planned, 2 % lidocaine jelly (1 – 2 mL) was placed within the nostril.

4. Topicalization was assessed as the absence of subject discomfort when key airway landmarks were stimulated:

- For oral fibreoptic intubations: stimulation of the uvula, tongue and bilateral posterior pharyngopalatine fauces with a wooden tongue blade.
- For nasal fibreoptic intubations: stimulation of the posterior nares at least 3 cm from the anterior os with a soft-tipped swab stick in addition to stimulation of the uvula, posterior tongue and bilateral posterior pharyngopalatine fauces with a wooden tongue blade.

It was anticipated that adequate topicalization and absence of a gag reflex would be evident within 15 minutes of beginning topicalization.

5. After insertion of the fibreoptic bronchoscope, additional doses of 2 % lidocaine in 1–2 mL aliquots were administered to the lower airway via the working channel of the bronchoscope. Subjects were asked to take slow regular deep breaths to facilitate distribution of local anaesthetic spray to the lower airway.

6. The maximum dose of topical lidocaine was limited to 4.5 mg/kg.

If a nasal intubation was planned and vasoconstriction was required, Afrin nasal spray could be administered. If Afrin was administered it was recorded on the concomitant medications CRF.

Rescue Midazolam

Rescue MDZ could be administered PRN in 0.5 mg doses IV up to 0.2 mg/kg for RSS score of 1. Rescue MDZ requirements were documented and recorded on the appropriate CRF.

Objectives

The primary efficacy variable was the percentage of subjects requiring rescue MDZ to achieve and/or maintain proper sedation levels (RSS score ≥2 throughout the study drug infusion.

Secondary efficacy variables were:

- Total dose of rescue MDZ required (mg) to achieve and/or maintain target sedation levels;
- Percentage of subjects requiring additional rescue medications other than MDZ to achieve and/or maintain target sedation levels;
- Anaesthetist assessment of ease of subject care;
- Subject recall and satisfaction assessed 24 hours post study drug.

Efficacy endpoints

Ramsay Sedation Scale

Subjects were assessed using the Ramsay Sedation Scale (RSS) at baseline, 15 minutes after start of study drug and every 3 minutes thereafter during drug infusion, at the end of topicalization, and prior to rescue medication administration (MDZ). The target score was RSS ≥ 2. RSS criteria are as follows:

Table 7. Ramsay Sedation Scale

Clinical Score	Level of Sedation
1	Patient is anxious and agitated or restless, or both.
2	Patient is cooperative, oriented and tranquil.
3	Patient responds to command only.
4	Patient exhibits brisk response to light glabellar (between the eyebrows) tap or loud auditory stimulus.
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6	Patient exhibits no response to stimulus.

The Ramsay Sedation Scale has been used and validated in intubated and non-intubated patients. This scale was also used in the pivotal clinical trials supporting the original MAA of DEX.

Anaesthetist Assessments

Immediately following discontinuation of study drug, prior to the scheduled surgery/procedure, the anaesthetist rated the ease of intubation, hemodynamic stability, and subject cooperation using Visual Analog Scales (VAS).

Subject Assessment

At the end of the 24-Hour Follow-Up Period, the subject was given a Subject Satisfaction Questionnaire so that the subject's recall of and satisfaction with the intubation procedure could be assessed. Subjects rated satisfaction with the placement of the breathing tube on a scale of 0 (not satisfied) to 10 (extremely satisfied).

Randomisation

In order to ensure balanced treatment allocation based on airway difficulty and physical status of the study subject, the randomization schedule was stratified based on both Mallampati classification (Class I-III vs. Class IV), and on ASA classification status (Class I-III vs. Class IV). When a subject was ready to be randomized, the site pharmacist obtained the subject's Mallampati classification and ASA Class from the PI prior to calling the IVRS to obtain the subject's treatment assignment.

With the goal of enrolling a minimum of 10 subjects in ASA IV, an enrollment cap was placed on ASA I-III subjects when the total number of ASA I-III subjects reached 90. Before the study was initiated, the telephone number and call-in instructions for the IVRS were provided to each site.

Subjects who met the selection criteria were randomized by the IVRS to receive either DEX or PBO within 24 hours of their scheduled surgery/procedure. Subject numbers were assigned by site, randomization numbers were assigned by IVRS, and each randomization number was unique. Randomization scheme and codes (subject identification and treatment assigned) are provided in the dossier.

Blinding

This was a double-blind study. All study personnel at the site, except the site pharmacist, were blinded to study drug assignment. The pharmacist received the bulk study drugs, and stored the supplies in a secure location. The pharmacist obtained the randomization assignment from the study IVRS after a new subject had been identified and a medication order had been written.

The pharmacist prepared the IVRS-assigned study drugs in identical containers. Labeling attached to each container identified the subject's unique identification number and initials. The labels affixed to the container did not include the subject's treatment assignment.

The unblinding of study subjects during the trial was not allowed unless there was a compelling medical or safety reason [e.g., knowledge of the blinded information was necessary for treatment of a serious adverse event (SAE)]. The unblinded Pharmacist was responsible for the security of the blinded randomization codes for the study. If it became necessary to break the blind, the PI was to contact the unblinded Pharmacist to obtain the specific treatment assignment for the subject in question. The sponsor was notified as soon as possible first by phone, then by fax, regarding the necessity of breaking the blinded code. The PI notified the IRB, as required. Also, the date, time the blind was broken, and the reason for breaking the blind was documented on the subject's Case Report Form (CRF).

Sample size

The sample sis of 90 subjects (45 DEX, 45 PBO) was based on the following assumptions: 80% power, less than 20% of subjects in the DEX group and more than 50% of subjects in the PBO group would require rescue MDZ for proper sedation during the study using a Fisher's exact test with alpha=5% (two-sided.

Statistical methods

All statistical analyses were performed using a two-sided 5% significance level. The ITT population was used as the primary population for efficacy analyses. The PP population was used as the secondary population for efficacy analyses. Since there was only one primary efficacy endpoint and one primary efficacy analysis, no adjustment for multiple comparisons was applied.

Primary analysis

The primary efficacy variable was the percentage of subjects requiring rescue MDZ to achieve and/or maintain proper sedation levels (RSS score ≥2) throughout the study drug infusion.

For the primary efficacy analysis, percentages of subjects in the two treatment groups who required rescue MDZ to achieve/maintain target sedation levels during study drug infusion, according to RSS criteria, were assessed using Fisher's exact test. Subjects who were randomized but did not receive any study drug were excluded from all safety and efficacy analyses. When a baseline value was missing prior to study drug infusion, the value obtained during the screening period was used as the baseline value. Otherwise, there was no imputation of missing data.

Secondary analyses

For the secondary analysis, the total dose of MDZ required to achieve/maintain target sedation levels was summarized descriptively by treatment group and differences were assessed using a one-way ANOVA with treatment as the factor. The number and percentage of subjects who required rescue medication other than MDZ during study drug infusion were summarized by treatment group and differences were assessed using Fisher's exact test.

Anesthesiologist ratings of the ease of intubation, hemodynamic stability and subject cooperation using Visual Analog Scales were summarized by treatment group, and assessed using a one-way ANOVA, with treatment as the factor. The Subject Satisfaction Questionnaires measuring the subject's recall of, and satisfaction with, the intubation procedure, were summarized by treatment group and differences were assessed using Fisher's exact test for categorical values and a one-way ANOVA for continuous variables.

The treatment effect of DEX on the primary endpoint and all secondary endpoints were also analyzed using the CMH test or an ANCOVA model, as appropriate, adjusted for the Mallampati classification (Mallampati status I-III vs. IV).

Results

Participant flow

A total of 124 subjects who met the eligibility criteria were randomized, with 63 in the DEX group and 61 in the PBO group. Eight subjects randomized to receive DEX and eleven randomized to receive PBO did not receive study drug, mostly because surgery was cancelled. These subjects were excluded from the safety and efficacy analyses.

55 subjects in the DEX group and 50 in the PBO group received a study drug infusion and were included in the safety/ITT analysis population. Only one subject (in the DEX group) who received study drug was excluded from the PP population. He received MDZ during study drug infusion while RSS was 2 (rescue MDZ was to be given only when RSS <2).

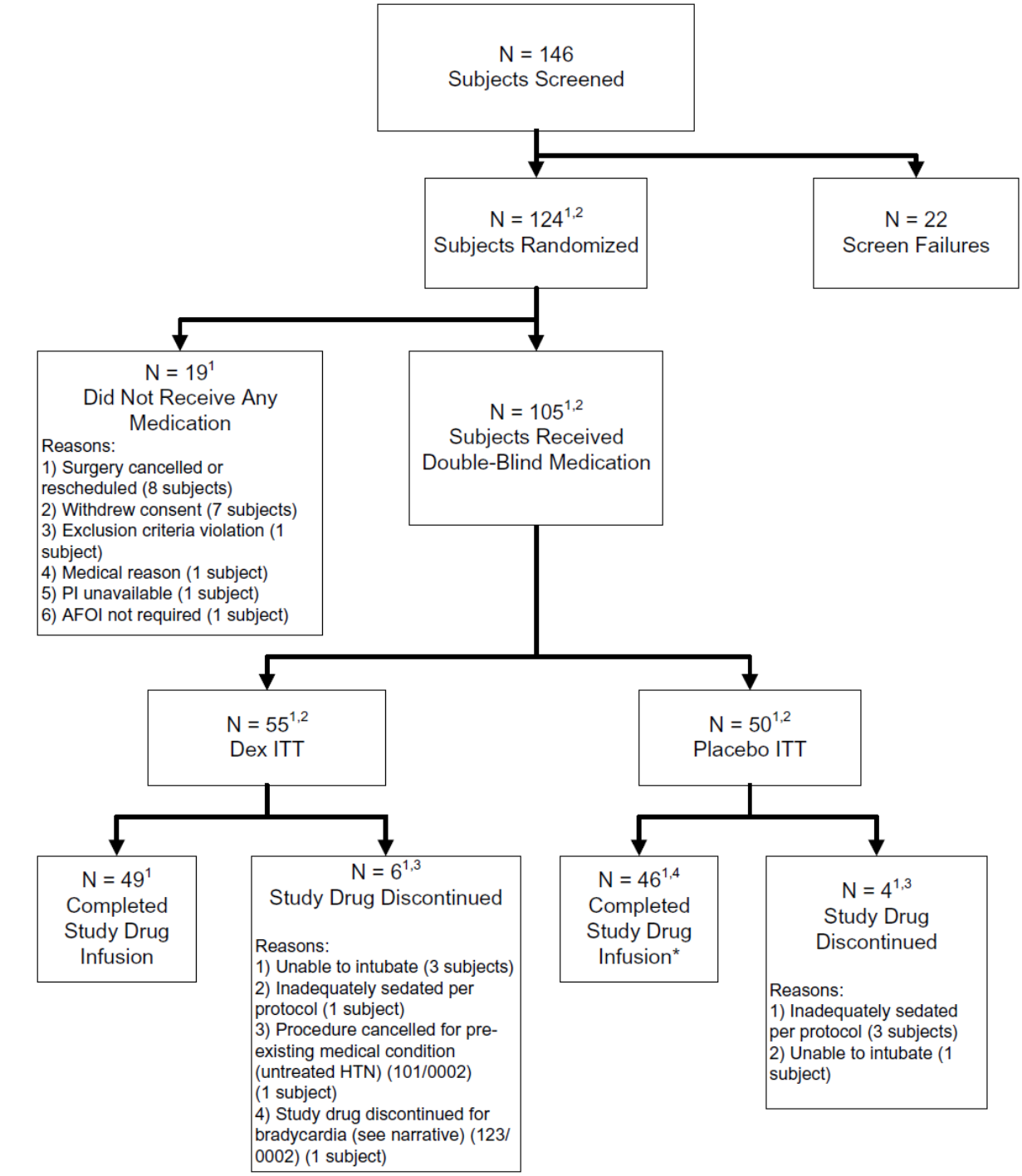
Of the 105 subjects (55 DEX group & 50 PBO group) in the safety/ITT population, 51 and 46 subjects respectively, completed the 24-hour follow-up. In the DEX group, 1 subject had surgery cancelled for pre-existing, untreated hypertension (narrative provided in Section 12.3.2 of the CSR); 2 were unable to be intubated and had surgery cancelled; and 1 was still intubated and sedated at the time of the 24-hour follow-up. In the PBO group, 2 subjects were lost to follow-up, 1 subject was heavily sedated and unable to respond at the 24- hour follow-up; and 1 was a treatment failure and received propofol.

Table 8. All Randomized Subjects

Classification	Number (%) of Subjects		
	DEX	PBO	All Subjects
All Randomized Subjects	63	61	124
Safety Population	55 (87.3%)	50 (82.0%)	105 (84.7%)
ITT Population	55 (87.3%)	50 (82.0%)	105 (84.7%)
PP Population	54 (85.7%)	50 (82.0%)	104 (83.9%)

- The Safety Population was defined as all patients who were randomized and received study drug.
- The Intent-to-treat (ITT) Population was defined as all patients who received study drug and also had at least one post-baseline efficacy measurement
- The Per Protocol Population was defined as all patients in the ITT Population who completed the study and had no major protocol violation.

Figure 2. Disposition of Subjects



1. Listing 16.2.1.1, Subject General Information, Randomized Population
2. Table 14.1.2, Summary of Subject Disposition, Randomized Population
3. Table 14.3.1.2.3 Subjects Discontinuing Study Drug Infusion Prematurely, PP Population
4. CRF for subject 115/0008

*One subject (115/0008) was inadequately sedated per protocol. Per protocol subject should have been discontinued, but subject was completed (protocol deviation).

Of the 55 subjects in the DEX group, 49 (89%) completed study drug infusion and were successfully intubated; and of the 50 subjects in the PBO group, 46 (92%) completed study drug infusion and were

successfully intubated (Table 9). Six (11%) subjects in the DEX group and 4 (8%) in the PBO group discontinued study drug infusion prematurely. The reasons for premature discontinuation of study drug infusion were:

- unable to intubate, 3 (5.5%) subjects in the DEX group and 1 (2.0%) subject in the PBO group,
- inadequate sedation by protocol allowed amounts of study drug and MDZ or required additional rescue medication other than MDZ: 1 (1.8%) subject in the DEX group and 3 (6.0%) subjects in the PBO group,
- other reasons (See narratives, CSR Section 12.3.2.2), 2 (3.6%) subjects in the DEX group and no subjects in the PBO group (see Figure 2 for the specific reasons).

Table 9. Disposition: All Treated Subjects

Safety / ITT Population (Subjects who received any study drug)	Number (%) of Subjects			
	DEX N=55 n (%)	PBO N=50 n (%)	Total N=105 n (%)	p-value
Completed Study Drug Infusion	49 (89.1)	46 (92.0)	95 (90.5)	–
Reason for Premature Discontinuation of Study Drug Infusion				
Any reason	6 (10.9)	4 (8.0)	10 (9.5)	–
Subject could not be successfully intubated	3 (5.5)	1 (2.0)	4 (3.8)	0.619
Subject could not be adequately sedated by protocol allowed amounts of study drug and MDZ or subjects required additional rescue medication other than MDZ	1 (1.8)	3 (6.0)	4 (3.8)	0.345
Other reason	2 (3.6)	0	2 (1.9)	0.496
Completed 24-hr Follow-up	51 (92.7)	46 (92.0)	97 (92.4)	–

The protocol deviations defined prior to data unblinding included improper dosing of study medication and use of prohibited concomitant medication. Details of significant protocol deviations are provided in the study report.

Baseline data

A summary of demographic and key baseline characteristic information for the all patients treated population is presented below.

Table 10. Demographics by Treatment Group (Safety Population)

Variable	DEX (N=55)	PBO (N=50)	p-value
Age (Years)	–	–	0.787
Mean (SD)	52.6 (14.14)	51.9 (15.27)	–
Range	21 – 78	19 – 77	–
Gender [n (%)]	–	–	0.222
Male	33 (60.0%)	36 (72.0%)	–
Female	22 (40.0%)	14 (28.0%)	–
Ethnic Origin [n (%)]	–	–	0.087
Caucasian	29 (52.7%)	37 (74.0%)	–
Black	10 (18.2%)	5 (10.0%)	–
Asian	0	0	–
Hispanic	16 (29.1%)	8 (16.0%)	–
Other	0	0	–
Weight (kg)	–	–	0.849
Mean (SD)	93.51 (29.81)	94.52 (23.89)	–
Range	46.7 – 203.2	44.0 – 147.7	–
Height (cm)	–	–	0.085
Mean (SD)	170.25 (10.86)	174.42 (13.63)	–
Range	150.0 – 196.9	145.0 – 223.5	–

Table 11. Subjects Receiving Prior Medication for Pre-existing Cardiovascular Disease (Safety Population)

Classification	Prior to Study drug Infusion	
	DEX N = 55 n (%)	PBO N = 50 n (%)
Any cardiovascular medication[a]	22 (40.0)	13 (26.0)
Agents acting on the renin-angiotensin system	11 (20.0)	13 (26.0)
Beta blocking agents	18 (32.7)	7 (14.0)
Calcium channel blockers	7 (12.7)	3 (6.0)
Diuretics	10 (18.2)	5 (10.0)

a Some subjects were taking multiple medications for cardiovascular disease.

Classification	DEX (N=55) n (%)	PBO (N=50) n (%)	p-value

ASA Classification	–	–	0.759
ASA I	1 (1.8)	3 (6.0)	–
ASA II	23 (41.8)	18 (36.0)	–
ASA III	25 (45.5)	26 (52.0)	–
ASA IV	6 (10.9)	3 (6.0)	–

Table 13. Baseline Ramsay Sedation Scores (ITT Population)

Ramsay Sedation Score (RSS)	**DEX (N=55) n (%)**	**PBO (N=50) n (%)**
RSS = 1 (subject was anxious and agitated or restless, or both)	15 (27.3)	16 (32.0)
RSS = 2 (subject was co-operative, oriented and tranquil)	40 (72.7)	34 (68.0)
RSS = 3 (subject responded to command only)	0	0
RSS = 4 (subject exhibited brisk response to light glabellar tap or loud auditory stimulus)	0	0
RSS = 5 (subject exhibited sluggish response to light glabellar tap or loud auditory stimulus).	0	0
RSS = 6 (Subject exhibited no response to stimulus)	0	0

Primary analysis of efficacy (ITT population)

The ITT population was used as the primary population for efficacy analyses. The PP population was used as the secondary population for efficacy analyses. As the PP population was almost identical to the ITT population (with only one less subject in the PP population) and the analysis results from the PP population were the same as those from the ITT population, only efficacy results based on the ITT population are presented in the following subsections. The single exclusion from the PP analyses did not affect the trial results to any meaningful extent. The results for the primary efficacy endpoint - percentage of subjects requiring rescue midazolam, are presented below.

Table 14. Number (%) of Subjects Requiring Rescue Midazolam (ITT Population)

Rescue MDZ/No Rescue MDZ	**DEX (N=55) n (%)**	**PBO (N=50) n (%)**	**p-value[b]**
Required Rescue MDZ[a]	26 (47.3%)	43 (86.0%)	<0.001[b]
Did Not Require Rescue MDZ	29 (52.7%)	7 (14.0%)	–

a Rescue MDZ was given (when RSS < 2) in 0.5 mg increments IV as needed (maximum 0.2 mg/kg) to achieve and/or maintain target RSS of ≥ 2.

b When Mallampati Class was included as a covariate in the exploratory analysis using CMH test, the p-value was similar (<0.001).

The percentage of subjects who required rescue MDZ to achieve and/or maintain the target sedation level of RSS ≥ 2 during study drug infusion was significantly lower in the DEX group (47.3%)

compared to 86.0% in the PBO group (p < 0.001). When Mallampati Class was included as a covariate in the exploratory analysis using Cochran-Mantel Haenszel (CMH) test, the results were similar (p <0.001)

Secondary analyses

Ramsay Sedation Scale

Ramsay Sedation Scale (RSS) scores, assessed 15 minutes after starting study drug, were as follows.

Table 15. RSS Scores Assessed 15 Minutes After Starting Study Drug (ITT Population)

RSS Score	DEX (N=55)	PBO (N=50)	p-value[a]
n	55	49	0.001
Mean (SD)	2.1 (0.84)	1.7 (0.52)	
Median	2.0	2.0	
Range	1 – 5	1 – 3	

a p-values based on one-way analysis of variance ANOVA.

Midazolam total dose required to achieve and/or maintain target sedation level

The total dose of rescue MDZ required to achieve and/or maintain the target sedation level (Ramsay Sedation Scale at least 2) by treatment group was as follows.

Table 16. Total Dose of Rescue Midazolam (ITT Population)

Total dose of MDZ rescue medication (mg)	DEX (N=55)	PBO (N=50)	p-value[a]
Mean (SD)	1.07 (1.541)	2.85 (3.014)	<0.001
Median	0.00	2.25	–
Range	0.0 - 7.0	0.0 - 19.5	–

a p-values based on one-way ANOVA.

Need for additional rescue medications other than MDZ to achieve and/or maintain target sedation levels

One subject in the DEX group and four subjects in the PBO group required rescue medication other than MDZ (p = 0.189). Subject (109-0002) in the DEX group received propofol and suxemethonium for induction of anaesthesia at the same time that the subject was intubated and study drug was discontinued. Two subjects in the PBO group received propofol and two more received fentanyl as additional rescue medication for sedation during the awake fibreoptic intubation.

Anaesthetist Assessments

Table 17. Anesthesiologists' Assessment Using Visual Analog Scale (ITT Population)

Anesthesiologist Assessment[a]	DEX (N=55) Mean (SD)	PBO (N=50) Mean (SD)	p-value[b]
n	53	49	
Ease of Intubation (cm)	3.16 (2.661)	3.00 (2.968)	0.771
Hemodynamic Stability (cm)	1.91 (1.636)	2.59 (2.505)	0.108
Subject Cooperation (cm)	2.53 (2.360)	3.41 (2.844)	0.090

a The Anesthesiologist assessment was performed using Visual Analog Scale (VAS) scores (cm). The VAS scores ranged from 0 to 10, with the most favorable outcome associated with the lowest score.

b p-values based on one-way ANOVA.

Subject Assessment

Table 18. Subjects' Assessment (ITT Population)

Question	Yes/No/ Missing	DEX (N=55)	PBO (N=50)	p-value[c]
Did you remember when the breathing tube was placed in your throat n (%)	Yes[b]	31 (60.8)	27 (57.4)	0.838
	No[b]	20 (39.2)	20 (42.6)	
	Missing	4	3	
Did you feel anxious during the time the tube was being placed in your throat n (%)	Yes[b]	27 (52.9)	22 (46.8)	0.686
	No[b]	24 (47.1)	25 (53.2)	
	Missing	4	3	
Anxiety[a] (n)	–	51	47	0.286
Mean (SD)	–	3.5 (3.95)	2.7 (3.28)	
Median	–	1.0	0.0	
Range	–	0 – 10	0 – 10	
Did you feel pain when the tube was being placed in your throat n (%)	Yes[b]	18 (35.3)	18 (38.3)	0.835
	No[b]	33 (64.7)	29 (61.7)	
	Missing	4	3	
Pain[a] (n)	–	51	47	0.958
Mean (SD)	–	1.6 (2.97)	1.6 (2.69)	
Median	–	0.0	0.0	
Range	–	0 – 10	0 – 10	
Satisfaction[a] (n)	–	50	47	0.316
Mean (SD)	–	7.5 (3.12)	8.1 (2.58)	
Median	–	9.0	9.0	
Range	–	0 – 10	0 – 10	

a Score was based on a 0-10 scale with 0 indicating no anxiety/no pain/not satisfied and 10 indicating extreme anxiety/worst pain ever experienced/extremely satisfied, respectively.

b Percentages were based on the number of subjects with non-missing values in the ITT population in each treatment group.

c For categorical data, p-value was based on Fisher's exact test; for continuous data, p-value was based on one-way ANOVA.

Subgroup Analyses

The treatment effect of DEX on the primary efficacy endpoint and secondary efficacy endpoints were evaluated by the Mallampati Class subgroups (Class I-III vs. Class IV), where Class IV correlates with greater difficulty of intubation.

Table 19. Number (%) of Subjects Requiring Rescue Midazolam by Mallampati Class (ITT Population)

Mallampati Class	Rescue MDZ/No Rescue MDZ	DEX (N=55) n (%)	PBO (N=50) n (%)
Mallampati Class I-III (n)		43	38
	Required rescue MDZ	22 (51.2)	32 (84.2)
	Did not require rescue MDZ	21 (48.8)	6 (15.8)
Mallampati Class IV (n)		12	12
	Required rescue MDZ	4 (33.3)	11 (91.7)
	Did not require rescue MDZ	8 (66.7)	1 (8.3)

Table 20. Total Dose of Rescue Midazolam Required by Mallampati Class (ITT Population)

Total dose of MDZ rescue medication	DEX (N=55)	PBO (N=50)
Mallampati Class I-III		
n	43	38
Mean (SD) (mg)	1.17 (1.603)	2.96 (3.388)
Median (mg)	0.50	2.25
Range (mg)	0.0 – 7.0	0.0 – 19.5
Mallampati Class IV		
n	12	12
Mean (SD) (mg)	0.71 (1.287)	2.50 (1.297)
Median (mg)	0.00	2.50
Range (mg)	0.0 – 4.0	0.0 – 4.5

Efficacy conclusions for AWAKE trial (2005-006)

DEX) was shown to be effective in providing and maintaining targeted sedation levels prior to and during awake fibreoptic intubation. The primary efficacy result showed a statistically significantly difference between the number of DEX and PBO treated subjects requiring rescue midazolam: 26 (47.3%) of DEX treated subjects required rescue MDZ versus 43 (86.0%) of PBO subjects (P< 0.001). This was supported by the secondary efficacy results (1) that the targeted sedation level (RSS ≥ 2) was achieved and maintained in these DEX-treated subjects prior to and during intubation, (2) the mean/median total dose of rescue MDZ required in the DEX-treated subjects was significantly lower than that in the PBO-treated subjects (1.07/0 mg vs. 2.85/2.25 mg), (3) no additional rescue medications other than midazolam were required to maintain sedation in the DEX-treated subjects, and (4) that the post-treatment anaesthetists' rating on ease of intubation, hemodynamic stability, and subjects cooperation, as well as subjects' rating on recall and satisfaction of the intubation procedure for the DEX-treated subjects were similar to those for the PBO-treated subjects where the majority received MDZ.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial MAC

Title: MAC study			
Study identifier	2005-005		
Design	Phase III, randomised, double-blind, placebo-controlled, multicentre study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		not reported not applicable not applicable
Hypothesis	Superiority		
Treatments groups	DEX 0.5 mcg/kg		Dexmedetomidine 0.5 mcg/kg. N=134 randomized
	DEX 1 mcg/kg		Dexmedetomidine 1 mcg/kg. N=129 randomized
	PBO		Placebo. N=63 randomized
Endpoints and definitions	Primary endpoint		Proportion of subjects not requiring MDZ for rescue sedation.
	Secondary endpoint		Total amount of rescue MDZ required
	Secondary endpoint		Time to the first dose of rescue MDZ
	Secondary endpoint		Proportion of patients who converted to alternative sedative or anaesthetic therapy
	Secondary endpoint		Time to recovery and readiness for discharge from PACU
	Secondary endpoint		Total amount of fentanyl required for pain control
	Secondary endpoint		Anaesthesiologists' assessment

	Secondary endpoint		Subjects' satisfaction and anxiety 24 hours after discontinuation of study drug
Database lock	Not reported		
Results and Analysis			
Analysis description	**Analyses**		
Analysis population	*Intent to treat* = all subjects who received the randomized study drug and had at least one post-baseline efficacy measure recorded		

Descriptive statistics and estimate variability	Treatment group	DEX 0.5 mcg/kg	DEX 1 mcg/kg	PBO
	Number of subjects[1]	134/129	129/123	63/57
	Requiring MDZ rescue (%)	59.7	45.7	96.8
	Variability statistic	*NA*	*NA*	*NA*
	Total dose MDZ (mean mg)	1.4	0.9	4.1
	SD	*1.69*	*1.51*	*3.02*
	Time to first MDZ (median minutes)	40.0	114.0	20.0
	Variability statistic	*NA*	*NA*	*NA*
	Time to discharge (median min)	29.0	25.0	14.0
	Variability statistic	*NA*	*NA*	*NA*
	Subjects' assessment of satisfaction (mean)	2.0	2.0	1.4
	SD	*0.97*	*0.97*	*1.39*
	Alternative sedative (%)	3.0	1.6	11.1
	Variability statistic	*NA*	*NA*	*NA*
	Anesthesiologists' assessment - Ease of maintenance (Mean)	2.8	2.2	4.4

	SD	*2.68*	*2.23*	*2.95*
Effect estimate per comparison	Primary endpoint: Requiring MDZ rescue	Comparison groups	DEX 1 mcg/kg vs. PBO	
		test statistic	*NA*	
		variability statistic	*NA*	
		P-value (CMH test)	<0.001	
	Secondary endpoint: Total dose MDZ (mean mg)	Comparison groups	DEX 1 mcg/kg vs. PBO	
		test statistic	*NA*	
		variability statistic	*NA*	
		P-value (1-way ANOVA)	<0.001	
	Secondary endpoint: Time to first MDZ (median minutes)	Comparison groups	<group descriptors>	
		test statistic	*NA*	
		variability statistic	*NA*	
		P-value (log-rank test)	<0.001	

[1]Treated/Completed study drug. NA = Not available/missing

Analysis performed across trials (pooled analyses and meta-analysis)

Patient groups and procedures in the MAC and AWAKE studies were rather different, including orthopaedic, ophthalmic, plastic, vascular stents, breast biopsies, AV fistulas and excision of lesions in the MAC study, and awake fiberoptic intubation prior to a surgical procedure in the AWAKE study, which made an additional pooled analysis unjustified.

Clinical studies in special populations

Patients with hepatic impairment were excluded from both pivotal studies and therefore no additional dosing information is provided for this population. Patients with renal impairment were allowed in both studies. However, a formal analysis of these patients was not performed due to the short term administration of the study drug during both studies. For the MAC study, the mean exposure to dexmedetomidine for the 0.5 mcg/kg and 1 mcg/kg loading dose groups was 97.0 and 102.3 minutes, respectively and for the AWAKE study, the mean exposure to dexmedetomidine was 37.7 minutes.

2.4.1. Efficacy Data from the Literature

Key supportive studies in monitored anaesthesia care from the literature

Arain et al (2002) investigated the effects of dexmedetomidine (1 mcg/kg loading dose over 10 minutes, maintenance 0.4-0.7 mcg/kg/h) vs. propofol (75 mcg/kg/min for 10 minutes, maintenance 12.5-75 mcg/kg/min) in 40 equally randomised patients scheduled for elective surgery (majority hip or knee surgery, 25% hernia repair, 10% other surgery) using regional anaesthetic blockade with an epidural, spinal or peripheral nerve block. The targeted sedation was achieved within 10 minutes with propofol and within 25 minutes with dexmedetomidine. Patients receiving dexmedetomidine during surgery had significantly lower pain scores in the postoperative period and received less morphine. Patients in each group performed similarly on the psychomotor testing and met discharge criteria at equivalent times. The 24-h follow-up inventory of patient satisfaction revealed that the sedation for their surgical procedure was equally satisfactory between groups.

Jalowiecki et al (2005) evaluated the effects in outpatient colonoscopy. 19 patients received DEX 1 mcg/kg over 15 min followed by an infusion of 0.2 mcg/kg/h, 21 patients received meperidine 1 mg/kg with midazolam 0.05 mg/kg and 24 patients received fentanyl 0.1-0.2 mg on demand. In all patients, endoscopy was completed with adequate pain relief. The level of analgesia was similar in all study groups. Fentanyl was administered in nine cases in both the DEX and meperidine-midazolam groups and to 19 patients in the fentanyl group. The average use of supplemental fentanyl was 0.04 mg in the meperidine-midazolam group, which was significantly lower than that in the DEX group (0.1 mg) and fentanyl group (0.18 mg). The average duration of colonoscopy was longer in the DEX group compared to the meperidine-midazolam and fentanyl groups (13 min, 9 min, 8 min, respectively, p = 0.0038). In the DEX group, the time required to reach home discharge readiness was longer compared with the meperidine-midazolam and fentanyl groups (85 min, 39 min, 32 min, respectively, p = 0.007). According to the study protocol, three patients from the DEX group were admitted to the hospital for 12-h observation because of safety concerns. The study was terminated before the planned 90 patients had been recruited because of adverse events among patients receiving DEX, in particular bradycardia (to approximately 40 bpm in 2 of 19 cases) and hypotension (to less than 50% of the initial value in 4 of 19 patients). The authors concluded DEX compared with commonly used sedation regimens was associated with the frequent requirement for supplemental fentanyl, sometimes profound hypotension and bradycardia, and prolonged recovery time. In their evaluation side effects may limit its usefulness in colonoscopy.

Brown et al (2006) retrospectively reviewed the records of 231 patients who underwent endovascular repair of abdominal aortic aneurysms. They reported the outcomes of a subset of 14 patients who underwent sedation with dexmedetomidine compared with 22 contemporaneous patients who underwent general anaesthesia.

McCutcheon et al (2006) conducted a double-blind randomised controlled trial to compare dexmedetomidine with conventional therapy (a mixture of midazolam and fentanyl) in patients undergoing carotid endarterectomy under regional anaesthesia. They enrolled 27 patients in the dexmedetomidine arm and 29 patients in the standard of care arm. Dexmedetomidine was administered at a loading dose of 0.5 mcg/kg over 10 minutes followed by a maintenance dose of 0.2-0.8 mcg/kg/h. The patients in the standard of care arm received 40 mcg fentanyl and 1 mg midazolam in bolus followed by repeated boluses of 20 mcg fentanyl and 0.5 mg midazolam. Sedation was effectively titrated to RSS range 2-4 in both groups, with 98% of all recorded RSS being within the target range. Significantly fewer patients required interventions for hypertension and/or tachycardia in

the dexmedetomidine group (40% vs. 72%). More patients in the dexmedetomidine group required haemodynamic drug interventions postoperatively (44% vs. 14%), and these were primarily for hypotension. The number of patients requiring no additional pain relief was significantly larger in the dexmedetomidine group (72% vs. 38%). The time between admission to the postoperative unit and readiness for discharge was similar in both groups (dexmedetomidine 97.3 min vs. standard of care 102.9 min). There was no difference in the surgeons' rating on operational conditions. The overall patient satisfaction was high, and there was no difference between groups in terms of the proportion of patients who reported feeling some discomfort during the procedure.

Kaygusuz et al (2008) reported a double-blind clinical study with 40 randomly allocated patients to dexmedetomidine or propofol in combination with fentanyl during extracorporeal shockwave lithotripsy.

Jense et al (2008) prospectively reviewed the safety and efficacy of dexmedetomidine as a sole sedative agent together with local anaesthesia in 14 patients who underwent laryngeal surgery.

Gupta et al (2014) randomised 90 patients, 30 in each group, scheduled for elective general, plastic or otorhinolaryngological surgeries. At least 15 minutes before local anaesthesia, the patients received 0.5 mcg/kg (DL) or 1 mcg/kg (DH) of dexmedetomidine, or equivalent volume of saline over 10 minutes as a loading dose, followed by a maintenance dose beginning at a rate of 0.6 mcg/kg/h and titrated between 0.2-1 mcg/kg/h to a target level of sedation (RSS score 3). Any patient having an RSS score less than 3 received IV midazolam at a 0.02 mg/kg dose repeatedly until the target RSS score was achieved. Fentanyl was used for pain control in 0.5 mcg/kg boluses as necessary. Significantly more patients required rescue midazolam in the saline group (26 out of 30 patients) than the DL (17 out of 30 patients) and DH (12 out of 30 patients) groups. The total dose of rescue midazolam was also significantly higher in the saline group than in the DL and DH groups (3.88 mg, 1.28 mg, 0.87 mg, respectively). The number of patients requiring rescue doses of fentanyl, as well as the mean rescue dose was significantly higher in the saline group compared to the DL and DH groups (number of patients, 25, 18, 11; mean fentanyl doses, 144.2 mcg, 84.8 mcg, 83.9 mcg, respectively). The targeted RSS level was achieved in a higher number of patients in the DL and DH groups compared to the placebo group (difference significant to placebo, non-significant between the DH and DL groups). Similarly, the targeted VAS score on pain, ≤ 3 on a 0-10 scale, was achieved in significantly more patients in the DL and DH groups compared to placebo, with a non-significant difference between the two dexmedetomidine groups. In the postoperative unit, sedation scores were significantly higher in more patients in the placebo group as compared to the DL and DH groups, and significantly higher in the DL group compared to the DH group. The postoperative pain score evaluated with VAS was under 3 in a greater number of patients in the placebo group than in the DL and DH groups ($p = 0.0001$). Similarly, a higher number of patients in the DL group achieved VAS < 3 than in the DH group ($p = 0.003$). Patient and surgeon satisfaction was better in both dexmedetomidine groups compared to the placebo group ($p = 0.03$ for patients, $p = 0.06$ for surgeons), and the differences were non-significant between the dexmedetomidine groups.

DEX as a sole sedative agent in small diagnostic and therapeutic procedures

ter Bruggen et al (2017) selected 35 articles for a systematic review to summarise the evidence from RCTs for the efficacy of DEX during small diagnostic and therapeutic procedures compared to other commonly used sedatives. Pain level and patient satisfaction were the primary outcomes for effectiveness. For IV use, the initial loading doses of dexmedetomidine ranged between 0.5-4.0 mcg/kg for 10 minutes, with 1.0 mcg/kg over 10 minutes being the most commonly used dose (20 out of 29 trials, 57%). Most of the trials also included a maintenance dose of dexmedetomidine, with infusion rates ranging between 0.1-2.0 mcg/kg/h, of which doses 0.1-0.5 mcg/kg/h were commonly used until the end of the procedure.

Placebo was the comparator in seven trials, including 379 patients. Studies and main characteristics of these trials are presented in the table below:

First author + year published	Procedure	Study population (age range in years)	Blinding	N	Intervention	Outcome parameter(s)	Results
Eskandr, 2014	Cataract surgery	Adults (18-70)	Yes	60	IV Dexmedetomidine + LA versus LA	Pain (VAS) Duration of procedure MAP HR	↓ ↓ ↓ ↓
Wang, 2014	Laser assisted in situ keratomileusis (LASIK)	Adults (18-31)	Yes	30	IV Dexmedetomidine (D) versus IV propofol (P) versus IV placebo	Patient satisfaction Operator satisfaction Recovery time MAP HR SpO2	Placebo<P/D* Placebo<P<D* P<D P<D<placebo* D<P<placebo* →
Zhang, 2013	Electro-chemotherapy	Adults (18-60)	Yes	60	IV Dexmedetomidine versus IN Dexmedetomidine versus IV/IN saline (C)	Rescue Duration of procedure SBP HR SpO2	IV < IN < C IV < IN < C IV/IN < C* IV/IN < C* →
Bergese, 2010	Awake fiberoptic intubation	Adults (≥ 18)	Yes	105	IV Dexmedetomidine versus IV Saline (placebo)	Rescue Patient satisfaction Operator satisfaction MAP HR SpO2	↓ ↑ ↑ ↓* ↓* →
Hashiguci, 2008	Upper gastro-intestinal endoscopy	Adults (38-54)	No	40	IV Dexmedetomidine (D) versus IV Midazolam (M) Versus unsedated (placebo)	Duration of procedure MAP HR SpO2	M<D<placebo D<M<placebo* D ≤ M/placebo* →
Erdusmus,	Cataract	Adults (>	Yes	44	IV		

↑ INCREASED VALUES COMPARED TO CONTROL GROUP
↓ DECREASED VALUES COMPARED TO CONTROL GROUP
→ UNCHANGED VALUES COMPARED TO CONTROL GROUP

IV = intravenous; IN = Intranasal; pain = pain during procedure; pain LA = pain from local anesthetic; LA = local anesthetic; VAS = Visual analogue scale (pain score); NRS = Numeric rating scale (pain score); MAP = mean arterial pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure HR = Heart rate; SpO2 =peripheral capillary oxygen saturation; RR = respiratory rate; Recovery time = time till patient is recovered after procedure; Aldrete = time until Aldrete score is 10; Rescue = rescue medication because current medication is not sufficient; Ramsey = Ramsey sedation scale; OAA/S = Observer's Assessment of Alertness/Sedation; BIS = Bispectral Index Score ; RASS = Richmond Agitation Sedation Scale

*Significant difference

DEX sedation for awake fiberoptic intubation

Zhou et al (2016) conducted a meta-analysis on 13 RCTs (including the AWAKE study), where dexmedetomidine was used as a sedative for awake intubation in adult patients. The pooled patient population included 591 patients, out of which 285 patients received dexmedetomidine.

Use of dexmedetomidine was associated with a higher Ramsay sedation scale score [mean difference (MD): 1.02, 95% CI 0.77–1.28], vocal cord movement score (MD = 0.72, 95% CI, 0.20–1.24), coughing scores (MD = 0.66, 95% CI, 0.10–1.22), limb movement scores (MD = 0.69, 95% CI, 0.47–0.91).

Another eight clinical trials is presented by the MAH, where DEX was used in awake fiberoptic intubation or flexible bronchoscopy since the meta-analysis by Zhou et al (2016) was published:

Goneppanavar et al (2015) evaluated the effects of midazolam and dexmedetomidine on patient's response to fiberoptic bronchoscopy. The patients received intravenously either midazolam 0.02 mg/kg (27 patients) or dexmedetomidine 1 mcg/kg (27 patients). The authors concluded that in fiberoptic bronchoscopy, under topical airway anaesthesia, dexmedetomidine at the 1 mcg/kg dose provided superior patient comfort and tolerance as compared to midazolam at the 0.02 mg/kg dose.

Mirkheshti et al (2017) reported a study to evaluate the effects of local DEX on sedation rate and hemodynamic changes in candidate patients for fiberoptic nasotracheal intubation randomly allocated into three groups receiving intravenous dexmedetomidine (1 mcg/kg over 10 minutes, 31 patients), local dexmedetomidine (1 mcg/kg combined with 5 mg/kg lidocaine, 32 patients), or lidocaine alone (32 patients). The dose of propofol used to reach the predetermined cerebral state index before sedation induction was significantly higher in the control group compared to both dexmedetomidine groups.

Sharma et al (2017) compared two different doses of DEX in combination with topical spray and airway blocks in a randomised way for awake orotracheal fibreoptic intubation in patients (n=60) undergoing elective cervical spine surgery with rigid cervical collar *in situ.* The patients received DEX either at a dose of 0.5 mcg/kg along with airway blocks or at a dose of 1 mcg/kg along with airway

blocks. Endoscopy and intubation time, patient tolerance, vocal cord and limb movement and satisfaction score did not differ significantly between the groups.

Li CW et al (2015) compared DEX-MDZ and sufentanil with MDZ for sedation for awake fiberoptic nasotracheal intubation in 50 patients with limited mouth opening. The scores of ease of the AFOI procedure, patient's reaction during AFOI, coughing severity, tolerance after intubation, recall of the procedure and discomfort during the procedure were comparable in both groups.

Chopra et al (2016) assessed in a randomised, double-blind, placebo-controlled study a small-dose DEX for conscious sedation during AFOI in simulated cervical spine injury patients. DEX 1 mcg/kg over 10 minutes was followed by maintenance infusion at 0.7 mcg/kg/h or normal saline at the same dose and rate. The number of patients was 50 in each group. The sedation was targeted to RSS score of ≥ 2 during AFOI. The total number of patients requiring MDZ and the mean dose of MDZ required to achieve targeted sedation (RSS ≥ 2) was significantly less in the DEX group compared to the placebo group ($p < 0.001$). Similarly, patient satisfaction score, heart rate, systolic, diastolic and mean arterial pressure and respiratory parameters were significantly better among patients sedated with DEX ($p < 0.001$). Postintubation arousability in the two groups was comparable. The authors concluded that DEX provided optimum sedation without compromising airway or hemodynamic instability with better patient tolerance and satisfaction for AFOI, while preserving patient arousability for the postintubation neurological assessment.

Xu et al (2016) compared the efficacy and safety of DEX (1 mcg/kg loading dose over 10 minutes followed by a continuous infusion of 0.7 mcg/kg/h) versus remifentanil (with a target-controlled infusion to achieve a plasma concentration of 2.5 ng/ml, increased to 3 ng/ml 10 minutes later) for sedation during awake intubation of 68 patients. First attempt success rate, a rescue MDZ dose and the duration of intubation did not differ between the groups. Patients receiving remifentanil were significantly more tolerant of the tracheal tube. The authors concluded that both DEX and remifentanil are effective sedatives for awake intubation. The patients sedated with remifentanil tolerated the tracheal tube better after intubation with moderately increased risk of desaturation.

Niyogi et al (2017) evaluated the efficacy of IV DEX on sedation, patient comfort and cardiovascular responses during AFOI in patients with cervical spondylotic myelopathy in a randomised, placebo-controlled, double-blinded study in 56 adult patients. The patients received a DEX infusion at a rate of 1 mcg/kg for the first 10 minutes followed by 0.5 mcg/kg/h or a 0.9% normal saline infusion in the same manner. Airway blocks with lignocaine were given to all patients before undergoing AFOI. The patients receiving DEX had an acceptable level of sedation (OAA/S: 20 to 17) with greater comfort and satisfaction (VAS: 40-60), compared to the control group (VAS: 50-90, $p < 0.001$).

Hassan et al (2017) reported a randomised, double-blind study to assess whether the addition of a small dose of fentanyl could improve the sedative criteria of DEX during AFOI, without the need to

increase the dose of DEX which may be associated with airway compromise. Patients in three groups, fifty patients each, received an infusion of 1 mcg/kg of DEX over 20 min, or 2 mcg/kg of DEX over 20 min, or 1 mcg/kg of DEX added to 1 mcg/kg of fentanyl over 20 min. Among patients who received the 2 mcg/kg DEX loading dose, the incidence of airway obstruction was higher than in the other two groups. Limb movement scores were higher among patients who received 1 mcg/kg of DEX alone compared to the other two groups. All groups were comparable as regard to fiberoptic intubation scores, coughing and vocal cord opening scores. The authors concluded that adding 1 mcg/kg of fentanyl to DEX 1 mcg/kg can prevent the risk of airway obstruction associated with higher doses of DEX while achieving the same favourable intubation scores.

2.4.1.1. Systematic review of literature comparing procedural sedation conducted with dexmedetomidine or propofol, and with dexmedetomidine or midazolam

The MAH conducted separate systematic reviews of the literature, including randomised trials in procedural sedations with dexmedetomidine or propofol, and with dexmedetomidine or MDZ in adult patient population. Studies, where dexmedetomidine, propofol or MDZ was given as part of intensive or critical care or where additional medication with sedative property was used were excluded. For the latter condition, two exceptions were made: if the additional medication was opioid and used for analgesia purpose as part of the standard sedation regimen (justified also with the dose), or if the purpose was for rescue. To characterise the efficacy, the following variables were collected: number of patients with successful sedation with/without rescue treatment, number of patients with unsuccessful sedation, duration of procedure, amount of additional analgesics used, patient satisfaction with the procedural sedation and with pain control, operator overall satisfaction, recovery time.

Efficacy of sedation with dexmedetomidine versus propofol

From the identified 290 publications in Pubmed, 130 publications in Embase database and 24 reviews in the Cochrane database, 19 trials met the selection criteria including 496 patients sedated with DEX and 501 patients sedated with propofol.

Procedures were surgical (486 patients), diagnostic (262 patients), other procedures like extracorporeal lithotripsy and fibreoptic intubation (132 patients) and with healthy volunteers (117 patients).

In all but the healthy volunteer studies dexmedetomidine sedation was initiated with a loading dose: in 12 studies the loading dose was 1 mcg/kg dexmedetomidine in 10 minutes, in the rest 0.5 mcg/kg over 5 or 10 minutes, or less. The maintenance doses varied between 0.2-0.7 mcg/kg/h with one exception where doses in the range of 0.2-1.4 mcg/kg/h were used (Cho et al 2015).

Fifteen trials reported patient numbers in terms of successful sedation with/without the use of rescue treatment (791 patients).

Table 3. Successful sedation without rescue medication, study and patient distribution, dexmedetomidine vs. propofol

% of patients with successful sedation without rescue medication	DEX		PRO	
	No. of studies	No. of patients	No. of studies	No. of patients
≥ 90%	9	200	9	207

50-89%	5	162	6	190
< 50%	1	32	0	0
Not reported	4	102	4	104

Table 4. Proportion of patients successfully sedated without rescue medication, dexmedetomidine vs. propofol

Reference	Type of procedure	% of patients successfully sedated without rescue medication	
		DEX	PRO
Kasuya 2009	Healthy volunteer experiment	100.0	100.0
Wang 2017	Inguinal hernia repair	100.0	100.0
Wang 2014	Eye surgery, laser in situ kertomielusis	100.0	100.0
Ma 2012	Upper airway procedure	96.7	76.7
Kaygusuz 2008	Lithotripsy	95.0	85.0
Tsai 2010	AFOI	95.0	95.0
Loh 2016	MRI	93.3	93.3
Takimoto 2011	Endoscopic tumour resection	93.3	93.3
Salem 2016	Lithotripsy	92.3	88.5
Nallam 2017	Ear surgery	88.0	56.0
Sriganesh 2015	Cerebral angiography	76.7	86.7
Kim 2015	Endoscopic surgery	72.4	90.0
Wu Y 2015	Endoscopy	57.6	67.6
Cho 2015	Endoscopy	50.0	100.0
Ebert 2016	Gastroscopy /esophageal endoscopy	3.1	100.0
Kim KN 2017	Hand surgery in regional anaesth	not reported	not reported
Sethi P 2015	Dilatation and curettage, gynecology	not reported	not reported
Frolich MA 2013	Pain perception, healthy volunteer	not reported	not reported
Frolich MA 2011	Hemodynamic test	not reported	not reported

Efficacy of sedation with dexmedetomidine versus midazolam

A total of 243 publications in Pubmed, 116 publications in Embase database and 20 reviews in the Cochrane database were listed after the literature search, 14 reports of which fulfilled all criteria,

including 546 and 543 patients sedated with dexmedetomidine or midazolam, respectively. The procedures were surgical (746 patients), diagnostic (248 patients), and with healthy volunteers (95 patients). In all but three trials (in a cataract surgery trial, and two trials with healthy volunteers), dexmedetomidine sedation was initiated with a loading dose: in 7 studies loading dose was 1 mcg/kg dexmedetomidine (among them in two trials up to this dose) over 10 minutes, (with one exception of 15 minutes). In the other trials the loading dose was 0.5 mcg/kg loading dose within 10 minutes, and in one trial the dexmedetomidine loading dose was 0.25 mcg/kg in 5 minutes.

Twelve trials reported patient numbers in terms of successful sedation with/without use of rescue treatment (994 patients).

Table 5. Successful sedation without rescue medication, patient and study distribution, dexmedetomidine vs. midazolam

% of patients with successful sedation without rescue medication	DEX		MDZ	
	No. of studies	No. of patients	No. of studies	No. of patients
≥ 90%	12	498	10	436
50-89%	0	0	1	30
< 50%	0	0	1	30
Not reported	2	48	2	47

Table 6. Proportion of patients successfully sedated without rescue medication, dexmedetomidine vs. midazolam

Reference	Type of procedure	% of patients successfully sedated without rescue medication	
		DEX	MDZ
Alhashemi 2006	Cataract surgery	100.0	100.0
Demiraran 2007	Upper endoscopy	100.0	100.0
Fan 2013	Dental surgery	100.0	100.0
Jo 2016	Elective lower limb surgery in spinal anaesth	100.0	100.0
Kaya 2010	Urology - TURP in spinal anaesth	100.0	100.0
Ustun 2006	Dental surgery	100.0	100.0
Liao 2012	Bronchoscopy	100.0	99.0
Apan 2009	Cataract surgery	100.0	96.7
Cheung 2007	Dental surgery	100.0	96.7
Mishina 2017	Hernia repair	100.0	91.8
Peng 2016	Lumbar disc surgery	90.0	70.0

Takimoto 2011	Endoscopic tumour resection	93.3	40.0
Frolich 2011	Hemodynamic test, healthy volunteer	not reported	not reported
Frolich 2013	Pain perception, healthy volunteer	not reported	not reported

Time to onset of sedation

Time to onset was reported with exact figures in six studies, in all of which except one the time to onset was shorter with propofol (Table and 37). The dexmedetomidine loading dose was given over 10 min in all studies.

Table 36. Time to onset of sedation, dexmedetomidine vs propofol

Reference	Type of procedure	Time to onset of sedation			Comparison	No. of patients		Dose		Comment
		DEX	PRO	Unit		Dex	PRO	DEX	PRO	
Wang 2017	Inguinal hernia repair	25.5	12.3	min	p = 0.001	40	40	0.5 mcg/kg + 0.5 mcg/kg/h	2 mg/kg + 1.5 mg/kg/h	Fentanyl 0.5 mcg/kg given both arms 5 min before procedure
Kim 2017	Hand surgery in regional anaesthesia	709.1	502.7	sec	p < 0.001	29	28	1 mcg/kg + 0.4 mcg/kg/h	TCI to 1.6 mcg/ml then to 0.2 mcg/ml target effect site cc	Time of onset to BIS 70: DEX, 809.3 sec, PRO 590.3 sec (p < 0.001)
Cho 2015	Endoscopy	47.4	32.7	min	p < 0.05	20	22	1 mcg/kg + 0.2-1.4 mcg/kg/h	TCI to 1 mcg/ml effect site cc	Remifentanil in both arms in 1.5 ng/ml effect site cc TCI
Sriganesh 2015	Cerebral angiography	15.4	2.3	min	p < 0.001	30	30	1 mcg/kg + 0.5 mcg/kg/h	1.5 mg/kg + 1.5 mg/kg/h	
Loh 2016	MRI	10.7	7.4	min	NS	15	15	1 mcg/kg + 0.2-0.7mcg/kg/h	1.5 mg/kg + 1.5 mg/kg/h	

Table 37. Time to onset of sedation, dexmedetomidine vs midazolam

Reference	Type of	Time to onset of	Comparis	No. of patients	Dose	Comment

	procedure	sedation			on					
		DEX	MDZ	Unit		DEX	MDZ	DEX	MDZ	
Peng 2016	Lumbar disc surgery	8.7	8.1	min	NS	30	30	0.5 mcg/kg in 10 min + 0.5 mcg/kg/h	0.05 mg/kg + 0.05 mg/kg/h	sedative + fentanyl 1 mcg/kg

Recovery times

Recovery times were reported in seven studies compared to PRO and in three studies compared to MDZ. Studies used different definitions and methods to measure the time.

Table 7. Recovery times, dexmedetomidine versus propofol

Reference	Type of procedure	No. of patients		Recovery score	Recovery time		Unit	Comment
		DEX	PRO		DEX	PRO		
Wang 2017	Inguinal hernia repair	40	40	Aldrete 10	8.9	5.6	min	p = 0.001
Kim 2017	Hand surgery in regional anaesthesia	29	28	OAA/S 5	580.9	478.8	sec	p = 0.07
				BIS 90	682.0	585.2	sec	p = 0.08
Sethi 2015	Dilatation and curettage, gynecology	25	25	Modified Aldrete 9-10	16.3	4.4	min	p < 0.05
Nallam 2017	Ear surgery	50	50	Aldrete 10	12.4	11.8	min	NS
Salem 2016	Lithotripsy	26	26	Kortilla's discharge criteria	87.5	85	min	NS
Kim 2015	Endoscopic surgery	29	30	Aldrete 9-10	21.2	20.4	min	NS
Sriganesh 2015	Cerebral angiography	30	30	Not available	8.7	8.4	min	NS

Recovery times compared to MDZ were reported in three studies. Each study applied different methods to measure recovery time. Details are shown in table Table 8.

Table 8. Recovery times, dexmedetomidine vs midazolam

Reference	Type of procedure	No. of patients		Recovery score	Recovery time		Unit	Comment
		DEX	MDZ		DEX	MDZ		
Alhashemi 2006	Cataract surgery	22	22	Aldrete 10	45	21	min	p < 0.01
Peng 2016	Lumbar disc surgery	30	30	Modified Aldrete score 9	8.9	9.2	min	NS
Demiraran 2007	Upper endoscopy	25	25	Kankaria recovery score	42	37.6	min	NS

Patients' and clinicians' satisfaction scores

Of the 12 studies evaluating the patients' overall satisfaction compared to PRO, the patients preferred DEX in 3 studies and propofol in 3 studies, while in 6 studies there was no significant difference in the scores. With regard to pain control, the patients' preference favoured DEX in 3 studies and PRO in 1 study, whereas the scores were not significantly different in 2 studies.

The clinicians were more satisfied with DEX sedation during the procedure in 5 studies, with PRO in 1 study, and neutral in 2 studies. In one of the latter two, MRI image quality was the primary variable.

In 10 studies comparing DEX to MDZ the patients/clinicians evaluated their satisfaction with the procedure, and in eight studies out of 10 the patients were asked about their satisfaction with pain control as well.

Regarding the patients' overall satisfaction with the sedation during the procedure, in three studies DEX was preferred, and in the other seven trials there was no significant difference in the patients' evaluation between DEX and MDZ. The patients' satisfaction with pain control showed a preference for DEX in two studies and in the other six studies the patients did not report a difference between the two sedatives.

The clinicians were more satisfied with DEX during the procedure in four studies, and did not find a difference in the four other studies.

Details of satisfaction scores are summarised in Table 10.

Table 9. Satisfaction scores, patients and clinicians dexmedetomidine vs propofol

Reference	Type of procedure	No. of patients		Patient satisfaction, overall		Satisfaction, pain control		Clinician satisfaction	
		DEX	PRO	Method	Preference	Method	Preference	Method	Preference
Nallam 2017	Ear surgery	50	50	VRS/Likert	DEX	VAS	DEX	VRS/Likert	DEX
Ma 2012	Upper airway procedure	30	30	VAS	DEX (in 3 out of 4 timepoints)	VAS	DEX		
Sethi 2015	Dilatation and curettage, gynecology	25	25	VRS/Likert	DEX			VRS/Likert	DEX
Wang 2017	Inguinal hernia repair	40	40	NRS/Likert	NS	NRS/Likert	DEX		
Kim 2017	Hand surgery in regional anaesthesia	29	28	VAS	NS			VAS	DEX
Wang 2014	Eye surgery, laser in situ kertomielusis	10	10	VRS/Likert	NS			Not classified	DEX
Kim 2015	Endoscopic surgery	29	30	VRS/Likert	NS			VRS/Likert	DEX
Salem 2016	Lithotripsy	26	26	Likert	NS	Likert	NS		

Reference	Type of procedure	No. of patients		Patient satisfaction, overall		Satisfaction, pain control		Clinician satisfaction	
		DEX	PRO	Method	Preference	Method	Preference	Method	Preference
Tsai 2010	AFOI	20	20	VRS/Likert	NS				
Kaygusuzy 2008	Lithotripsy	20	20			VAS	NS		
Loh 2016	MRI	15	15	VAS, Spielberger Strait Test Anxiety Inventory (STAI)	PRO			Image quality assessment in 5 grades	NS
Wu Y 2015	Endoscopy	33	34	VAS	PRO			VAS	NS
Eberl 2016	Gastroscopy / oesophageal endoscopy	32	31	Combined score	PRO	Included in the combined score	PRO	Combined score	PRO

VRS = verbal rating scale, NRS = numeric rating scale

Table 10. Satisfaction scores, patients and clinicians, dexmedetomidine vs midazolam

Reference	Type of procedure	No. of patients		Patient satisfaction, overall		Satisfaction, pain control		Clinician satisfaction	
		DEX	MDZ	Method	Preference	Method	Preference	Method	Preference
Alhashemi 2006	Cataract surgery	22	22	VRS/Likert	DEX	VRS/Likert	DEX	VRS/Likert	DEX

Reference	Type of procedure	No. of patients		Patient satisfaction, overall		Satisfaction, pain control		Clinician satisfaction	
		DEX	MDZ	Method	Preference	Method	Preference	Method	Preference
Ustun 2006	Dental surgery	20	20	VAS	DEX	VAS	NS	VRS/Likert	DEX
Fan 2013	Dental surgery	30	30	VAS	DEX			VRS/ Likert	
Demiraran 2007	Upper endoscopy	25	25	VAS	NS	VAS	NS	VAS	DEX
Mishina 2017	Hernia repair	99	97	Likert	NS	Likert	NS	Likert	DEX
Apan 2009	Cataract surgery	30	30	Binary rating	NS	VAS	DEX	VRS/Likert	NS
Cheung 2007	Dental surgery	30	30	NRS	NS	NRS	NS	NRS	NS
Kaya 2010	Urology - TURP in spinal anaesth	25	25	Binary rating	NS	VAS	NS	VRS/Likert	NS
Liao 2012	Bronchoscopy	99	99	Binary rating	NS	VAS	NS	VAS	NS
Peng 2016	Lumbar disc surgery	30	30	VRS	NS				

VRS = verbal rating scale; NRS = numeric rating scale

Clinical information relevant to dosing recommendations

MAC study

A dose-response effect with regard to the primary endpoint was demonstrated, as fewer patients required rescue MDZ for sedation with the DEX 1 mcg/kg dose (45.7%) than with the DEX 0.5 mcg/kg dose (59.7%). The mean total dose of rescue MDZ used to achieve and/or maintain the targeted sedation level was lower in the DEX 1 mcg/kg group (0.9 mg, SD 1.51) than the DEX 0.5 mcg/kg group (1.4 mg, SD 1.69). The median time to first rescue dose MDZ was longer for the DEX 1 mcg/kg group (114 minutes) than for the DEX 0.5 mcg/kg group (40.0 minutes). The percentage of patients who required rescue fentanyl for pain during the infusion period was lower for the DEX 0.5 mcg/kg group (59.0%) compared with the DEX 1 mcg/kg group (42.6%).

There were no significant differences in the need for MDZ rescue in either dose group regarding the age of DEX patients when comparing either <65 years to ≥65 years or <65 years to ≥75 years. There was a general trend to decreased total dose MDZ rescue with increased patient age in both dose groups. There was a significant difference in the proportion of patients with ophthalmic surgeries when comparing patients <65 years to ≥65 years and the ophthalmic surgery category consistently required less need for rescue MDZ and less mean total amount of rescue MDZ compared to other surgery types. The lower need for rescue and the lower doses required for rescue with increasing age appear to be related to the increased proportion of a surgery subtype that requires less need for and amount of MDZ rescue rather than a primary age effect.

AWAKE study

The primary endpoint results showed that fewer patients in the DEX (47.3%) than the PBO (86.0%) group required MDZ for rescue sedation ($p < 0.001$). The mean total dose of rescue MDZ required was significantly lower in the DEX-treated patients (1.07 mg, SD 1.54) than in the PBO-treated patients (2.85 mg, SD 3.01).

Literature

In 16 of 19 trials with PRO as comparator a DEX loading dose was used, in 12 studies with 1 mcg/kg injected in 10 minutes. In four studies the loading dose was under 1 mcg/kg.

Table 11. Dosing in the DEX-PRO literature review selection - all studies

Reference	**Type of procedure**	**Dose**		**Age (years)[a]**		**No. of patients**	
		DEX	**PRO**	**DEX**	**PRO**	**DEX**	**PRO**
Wang 2017	Inguinal hernia repair	0.5 mcg/kg 10 min + 0.5 mcg/kg/h	2 mg/kg + 1.5 mg/kg/h	68.5 (13.6)	66.9 (14.1)	40	40
Kim 2017	Hand surgery in regional anaesth	1 mcg/kg 10 min + 0.4 mcg/kg/h	TCI 1.6 mcg/ml target site effect cc with later increments in 0.2 mcg/ml	47.8 (15.2)	45.5 (14.3)	29	28
Wang 2014	Eye surgery, laser in situ	0.3 mcg/kg 10 min	56+[0.25· weight in kg]–[0.53·age in	25.0 (6.4)	25.2 (5.7)	10	10

Reference	Type of procedure	Dose		Age (years)[a]		No. of patients	
		DEX	PRO	DEX	PRO	DEX	PRO
	kertomielusis		years] mg				
Nallam 2017	Ear surgery	1 mcg/kg 10 min + 0.4 mcg/kg/h	0.75 mg/kg + 0.025 mg/kg/min	33.2 (8.4)	34.7 (9.2)	50	50
Ma 2012	Upper airway procedure	1 mcg/kg 10 min + 0.7 mcg/kg/h	TCI to 1.5 mcg/ml effect site cc, uptitrated in 0.2 mcg/ml increments, final mean cc 1.7 mcg/ml	50.6 (12.0)	48.1 (13.2)	30	30
Tsai 2010	AFOI	1 mcg/kg 10 min	TCI to 3 mcg/ml target effect site cc, adjusted with 1 mcg/ml as necessary	55.7 (9.0)	54.4 (6.8)	20	20
Salem 2016	Lithotripsy	1 mcg/kg 10 min + 0.3 mcg/kg/h	1 mg/kg + 3 mg/kg/h	48 (7)	46 (8)	26	26
Kaygusuz 2008	Lithotripsy	1 mcg/kg 10 min + 0.2 mcg/kg/h	1 mg/kg + 2.4 mg/kg/h	38 (8)	35 (9)	20	20
Sethi 2015	Dilatation and curettage, gynecology	1 mcg/kg 10 min + 0.5 mcg/kg/h	1.5 mg/kg	40 (11)	42 (14)	25	25
Eberl 2016	Gastroscopy / esophageal endoscopy	1 mcg/kg 10 min + 0.7-1 mcg/kg/h	TCI to 2 mcg/ml plasma cc	18 - >80	18 - >80	32	31
Cho 2015	Endoscopy	1 mcg/kg 10 min + 0.2-1.4 mcg/kg/h	TCI to 1 mcg/ml effect-site cc uptitrated to 1.5 mcg/ml	40.8 (11.8)	41.7 (12.8)	20	22
Kim 2015	Endoscopic surgery	0.5 mcg/kg 5 min + 03-0.7 mcg/kg/h	0.5 mg/kg + 30 mcg/kg/min	62.1 (10.3)	62.9 (12.3)	29	30

Reference	Type of procedure	Dose		Age (years)[a]		No. of patients	
		DEX	PRO	DEX	PRO	DEX	PRO
Wu Y 2015	Endoscopy	1 mcg/kg 10 min + 0.5 mcg/kg/h	0.6 mg/kg + 10-20 mg bolus	40.4 (11.6)	39.0 (14.4)	33	34
Takimoto 2011	Endoscopic tumour resection	0.25 mcg/kg 5 min + 0.4 mcg/kg/h	5 mg + 3 mg/kg/h	52-80	47-79	30	30
Loh 2016	MRI	1 mcg/kg 10 min + 0.2-0.7 mcg/kg/h	TCI, 1.5 mcg/ml titrated in 0.1 mcg/ml increments, final mean dose 2.1 mcg/ml	49.1 (18.0)	45.4 (14.6)	15	15
Sriganesh 2015	Cerebral angiography	1 mcg/kg 10 min + 0.5 mcg/kg/h	1.5 mg + 1.5 mg/kg/h	49.0 (10.7)	49.0 (11.4)	30	30
Frolich 2013	Pain perception, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 0.4, 0.8, 1.2, 1.6 mcg/ml plasma cc	24.7 (4.5)	24.5 (4.6)	28	31
Frolich 2011	Hemodynamic test, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 0.1, 0.2, 0.4, 0.8 mcg/ml plasma cc	21-55	21-55	20	20
Kasuya 2009	BIS and OAA/S comparison, healthy volunteers	TCI, to 0.6,1.2, 2.4 ng/ml plasma cc	TCI to 1, 2, 4 mcg/ml effect site cc	24 (4)	24 (4)	9	9

[a] Values are presented as mean (SD) or range.

Among the trials comparing the efficacy of dexmedetomidine to MDZ 11 studies out of 12 used a loading dose, in seven a 1 mcg/kg dose was applied for loading. The duration of the 1 mcg/kg loading dose was 10 minutes in five studies, in one study the loading time was 15 min, and in one study the dose was defined as 0.1 mcg/kg/min, without an upper time limit. In four studies a loading dose of 0.5 mcg/kg or less was used.

Table 12. Dosing in the DEX-MDZ literature review selection - all studies

Reference	Type of procedure	Dose		Age (years)[a]		No. of patients	
		DEX	MDZ	DEX	MDZ	DEX	MDZ
Mishina 2017	Hernia repair	0.5 mcg/kg in 10 min + 0.4 mcg/kg/h	2 mg	66.5 (11.7)	65.2 (11.6)	99	97
Jo 2016	Elective surgery (knee, tibiofibular, ankle, foot) in spinal anaesthesia	1 mcg/kg in 10 min + 0.5 mcg/kg/h	0.05 mg/kg + 0.025 mg/kg/h	47.1 (15.2)	47.0 (16.2)	58	58
Peng 2016	Lumbar disc surgery	0.5 mcg/kg in 10 min + 0.5 mcg/kg/h	0.05 mg/kg + 0.05 mg/kg/h	43.1 (10.1)	44.3 (11.4)	30	30
Apan 2009	Cataract surgery	no loading dose, 0.25 mcg/kg/h	25 mcg/kg/h	65.7 (11.3)	65.8 (11.8)	30	30
Alhashemi 2006	Cataract surgery	1 mcg/kg in 10 min + 0.1-0.7 mcg/kg/h	20 mcg/kg + 0.5 mg in boluses	34-79	40-75	22	22
Fan 2013	Dental surgery	0.1 mcg/kg/min until adequate sedation + 0.2 mcg/kg/h	0.005 mg/kg/min until adequate sedation + 0.01 mg/kg/h	26 (7)	29 (9)	30	30
Cheung 2007	Dental surgery	up to 1 mcg/kg in 10 min	5 mg	25.5 (4.2)	27.7 (7.1)	30	30
Ustun 2006	Dental surgery	1 mcg/kg in 15 min	0.1 mg/kg	17-28	17-28	20	20
Liao 2012	Bronchoscopy	1 mcg/kg in 10 min + 0.5 mcg/kg/h	2 mg + 1 mg in bolus as needed	58.5 (9.1)	60.1 (8.4)	99	99
Kaya 2010	Urology - TURP in spinal anaesth	0.5 mcg/kg in 10 min	0.05 mg/kg	56.6 (8.5)	54.8 (6.4)	25	25
Takimoto 2011	Endoscopic tumour resection	0.25 mcg/kg in 5 min + 0.4 mcg/kg/h	0.1 mg/kg + 1 mg in bolus as needed	52-80	48-80	30	30
Demirar	Upper	1 mcg/kg in 10	0.07 mg/kg	42.2	43.3	25	25

an 2007	endoscopy	min + 0.2 mcg/kg/h		(14.4)	(13.2)		
Frolich 2013	Pain perception, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 10, 20, 40, 80 ng/ml plasma cc	24.7 (4.5)	24.5 (4.6)	28	27
Frolich 2011	Hemodynamic test, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 10, 20, 40, 80 ng/ml plasma cc	21-55	21-55	20	20

[a] Values are presented as mean (SD) or range.

2.4.1.2. Discussion of published efficacy studies with DEX in procedural sedation

There is extended literature on the use of dexmedetomidine for procedural sedation. Publications differ in many ways, including study population, sample size, dosing protocol, and primary and other endpoints, which affect the value of the reported observations. In the review of the literature and the selection of publications, the primary aim was to present the efficacy data in the literature in a balanced way. Systematic reviews and meta-analyses were preferred, as they are by nature free of subjective selection bias in regard to how and which publications are chosen. The fact that systematic reviews are already available for the proposed indication, indicates a matured publication history of dexmedetomidine in procedural sedation. The literature search for this application was closed on 31 Oct 2017. Based on the literature search, two systematic reviews were conducted to compare the efficacy of dexmedetomidine to propofol and midazolam. Although there are published reviews in this regard, the aim was to present the most up-to-date data for these comparisons.

The most recent systematic review about dexmedetomidine as sole sedative agent in procedural sedation has been published by ter Bruggen et al (2017). The efficacy of dexmedetomidine was evaluated in small diagnostic and therapeutic procedures reported from randomised controlled trials in comparison to placebo, propofol, midazolam and opioids. Literature search was closed at the end of March 2014. Surgeries belonged to ophthalmic, ear, nasal, oral, dental and gynecological procedures, endoscopies and awake fibreoptic intubation. The primary efficacy outcomes included patients' satisfaction and pain level. The intranasal and intramuscular routes of administration and the paediatric use were discussed in the review but they are out of the focus of this application. Twenty nine adult studies with intravenous administration were identified, one of which had both intravenous and intranasal dexmedetomidine arms (19 and 20 patients, respectively) (Zhang et al 2013). The most common initial loading dose was 1.0 mcg/kg over 10 minutes (20 trials), ranging from 0.5 to 4.0 mcg/kg. Most of the trials also included a maintenance dose of dexmedetomidine, with infusion rates ranging between 0.1 and 2.0 mcg/kg/h, of which doses 0.1-0.5 mcg/kg/h were commonly used until the end of the procedure. The review stratified the studies by comparator: placebo, propofol, midazolam and opioids.

<u>Dexmedetomidine compared to placebo</u>

Seven trials with placebo-controlled design were identified. One in this group was the publication about the AWAKE study by Bergese et al (2010). Not counting the AWAKE report, four trials were in

ophthalmic surgery, the others were gastrointestinal endoscopy, and electrochemotherapy), altogether representing 274 patients. Patient satisfaction improved significantly in two out of three trials), operator satisfaction improved significantly in two out of two trials (where these variable were reported). The need for rescue medication was reported to be less in the dexmedetomidine arm in the two trials where this outcome was recorded. In three out of four trials the duration of procedure was shorter with dexmedetomidine (however, differences were not significant), and similar durations were reported in one trial.

Dexmedetomidine compared to opioids

Five trials were included in this comparison, representing 223 patients. Three studies reported on awake fibreoptic intubation procedures (including 110 patients), one on vaginal surgery and one on colonoscopy. Fentanyl was the comparator sedative in three studies, while remifentanil and sufentanil were the comparators in one study each. Patient satisfaction was significantly higher with dexmedetomidine in three of the four trials assessing this variable, and each of the three studies was conducted in awake fibreoptic intubation. Pain level was significantly lower in one out of three trials. There was no preference in the operators' satisfaction in any reports. All of the five trials measured procedure duration, which was significantly shorter with dexmedetomidine in one, and with fentanyl in another study. Only one of two trials assessing recovery time showed a significantly prolonged time in the dexmedetomidine group.

Dexmedetomidine compared to propofol

Propofol was compared to dexmedetomidine in nine trials (all IV applications), including 421 patients. The procedures included ophthalmic surgeries (n=4), upper airway surgery, oral and nasals surgeries, awake intubation and upper endoscopy.. Among the seven trials reporting patient satisfaction, five showed significantly higher satisfaction with dexmedetomidine, and two trials reported no difference. In three trials, there was a significantly lower level of pain in the dexmedetomidine group. Operator satisfaction was recorded in two studies, in one dexmedetomidine was preferred, and no difference was reported in the other. Duration of procedure did not differ significantly in the seven trials assessing this parameter. Recovery time was significantly shorter with dexmedetomidine in one, and with propofol in another, among the six reports with this variable.

Dexmedetomidine compared to midazolam

There are 11 trials, including 714 patients, in this comparison. The trials covered four dental surgeries, two upper and one lower gastrointestinal endoscopy, one bronchoscopy, one ophthalmic and one otologic surgery, and one shockwave lithotripsy in outpatient settings. Eight trials recorded patient satisfaction, in four studies dexmedetomidine achieved significantly better patient satisfaction, while in one trial midazolam was preferred. Four trials measured patient pain scores separately, and out of them in one trial dexmedetomidine, and in another midazolam-fentanyl combination provided better pain relief; there was no difference in two trials. Operators had significantly higher satisfaction with dexmedetomidine sedation in two out of six trials, no preference to either sedative in the other four. One trial out of ten showed a significantly prolonged duration of procedure with dexmedetomidine. Recovery time was significantly longer with dexmedetomidine in four out of the five trials which reported recovery time.

Systematic review comparing dexmedetomidine to propofol and midazolam in procedural sedation

The trials included in the systematic review represent a wide variety of procedures with ~1000 patient population in each comparison. Success rates of sedation with dexmedetomidine were high and comparable to the rates with propofol and midazolam. The duration of procedures did not differ except in one study in which dexmedetomidine sedation was favoured. Time to onset of sedation and recovery times were usually shorter with propofol and midazolam; however, only in part of the trials these periods were recorded. The additional analgesia use and post-procedural analgesia need were reported also in few studies only, with a tendency to a less need, and with longer time to the first postoperative analgesia demand, if sedated with dexmedetomidine. The patient and clinician satisfaction was reported in ~70% of the trials. The patients' overall satisfaction was well balanced, while showed a tendency to prefer dexmedetomidine regarding the efficacy of pain control. The clinicians' preference pointed toward dexmedetomidine sedation more often than comparators. In our overall evaluation, the efficacy of dexmedetomidine is comparable to propofol and midazolam, with additional benefit in pain control, and with slightly longer time regarding the onset of sedation and recovery.

2.4.2. Clinical Information Relevant to Dosing Recommendations

The MAC study included 2 DEX loading dose groups of 0.5 mcg/kg and 1 mcg/kg given over 10 minutes. Each was followed by a maintenance infusion of DEX initiated at 0.6 mcg/kg/h titrated between 0.2 to 1 mcg/kg/h to achieve and/or maintain the desired level of sedation (OAA/S □ 4). The 0.5 mcg/kg load arm was included to maintain the blindness of the study and additionally to provide a dosing benchmark. There were trends in the study results that favoured the loading dose of 1 mcg/kg over 0.5 mcg/kg. A dose-response effect with regard to the primary endpoint was demonstrated, as fewer patients required rescue MDZ for sedation, at a smaller dose, given later with the DEX 1 mcg/kg loading dose than with the DEX 0.5 mcg/kg loading dose. The percentage of patients who required rescue fentanyl for pain during the infusion period in the MAC study was significantly lower for both of the DEX groups compared to PBO (88.9%), but slightly higher for the DEX 0.5 mcg/kg group (59.0%) compared with the DEX 1 mcg/kg group (42.6%). The subgroup analyses in the MAC study also support the efficacy of the DEX 1 mcg/kg loading dose. No specific dosing recommendations with regard to age are required for efficacy.

The dosing in the AWAKE study included a DEX load of 1 mcg/kg given over 10 minutes followed by a fixed maintenance infusion of DEX at 0.7 mcg/kg/h. The results from this study also support the efficacy of the DEX 1 mcg/kg loading dose.

Patients with hepatic impairment were excluded from both studies and therefore no additional dosing information is provided for this population. Patients with renal impairment were allowed in both studies. However, a formal analysis of these patients was not performed due to the short term administration of the study drug during both studies.

In the literature the 1 mcg/kg loading dose followed by 0.2-1 mcg/kg maintenance dose, in awake intubation followed by 0.7 mcg/kg maintenance dose is the most often applied doses for DEX in this indication. Compared in few trials, the 1 mcg/kg loading dose brought benefits versus lower or higher loading doses, i.e. in terms of patient satisfaction, comfort, more favourable OAA/S scores, or lower incidence in adverse effects, respectively.

Results from MAC and AWAKE indicate that the DEX 1 mcg/kg loading dose was efficacious for sedation of non-intubated patients undergoing all procedures, as well as, prior to and during awake fiberoptic intubation. However, the DEX 0.5 mcg/kg dose may be suitable for less invasive procedures

such as ophthalmic surgery. Following the load, maintenance dosing of dexmedetomidine should generally be initiated at 0.6 mcg/kg/h and titrated to achieve the desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/h. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. With regard to awake fiberoptic intubation, a fixed maintenance dose of 0.7 mcg/kg/h was shown to be efficacious. Orion, Hospira and Abbot have not tested the efficacy and safety of a loading dose above 1 mcg/kg over 10 minutes.

Available data in the literature support the benefits of this dosing.

Table 13. Dosing in the DEX-PRO literature review selection - all studies

Reference	**Type of procedure**	**Dose**		**Age (years)[a]**		**No. of patients**	
		DEX	**PRO**	**DEX**	**PRO**	**DEX**	**PRO**
Wang 2017	Inguinal hernia repair	0.5 mcg/kg 10 min + 0.5 mcg/kg/h	2 mg/kg + 1.5 mg/kg/h	68.5 (13.6)	66.9 (14.1)	40	40
Kim 2017	Hand surgery in regional anaesth	1 mcg/kg 10 min + 0.4 mcg/kg/h	TCI 1.6 mcg/ml target site effect cc with later increments in 0.2 mcg/ml	47.8 (15.2)	45.5 (14.3)	29	28
Wang 2014	Eye surgery, laser in situ kertomielusis	0.3 mcg/kg 10 min	56+[0.25· weight in kg]–[0.53·age in years] mg	25.0 (6.4)	25.2 (5.7)	10	10
Nallam 2017	Ear surgery	1 mcg/kg 10 min + 0.4 mcg/kg/h	0.75 mg/kg + 0.025 mg/kg/min	33.2 (8.4)	34.7 (9.2)	50	50
Ma 2012	Upper airway procedure	1 mcg/kg 10 min + 0.7 mcg/kg/h	TCI to 1.5 mcg/ml effect site cc, uptitrated in 0.2 mcg/ml increments, final mean cc 1.7 mcg/ml	50.6 (12.0)	48.1 (13.2)	30	30
Tsai 2010	AFOI	1 mcg/kg 10 min	TCI to 3 mcg/ml target effect site cc, adjusted with 1 mcg/ml as necessary	55.7 (9.0)	54.4 (6.8)	20	20

Reference	Type of procedure	Dose		Age (years)[a]		No. of patients	
		DEX	PRO	DEX	PRO	DEX	PRO
Salem 2016	Lithotripsy	1 mcg/kg 10 min + 0.3 mcg/kg/h	1 mg/kg + 3 mg/kg/h	48 (7)	46 (8)	26	26
Kaygusuz 2008	Lithotripsy	1 mcg/kg 10 min + 0.2 mcg/kg/h	1 mg/kg + 2.4 mg/kg/h	38 (8)	35 (9)	20	20
Sethi 2015	Dilatation and curettage, gynecology	1 mcg/kg 10 min + 0.5 mcg/kg/h	1.5 mg/kg	40 (11)	42 (14)	25	25
Eberl 2016	Gastroscopy / esophageal endoscopy	1 mcg/kg 10 min + 0.7-1 mcg/kg/h	TCI to 2 mcg/ml plasma cc	18 - >80	18 - >80	32	31
Cho 2015	Endoscopy	1 mcg/kg 10 min + 0.2-1.4 mcg/kg/h	TCI to 1 mcg/ml effect-site cc uptitrated to 1.5 mcg/ml	40.8 (11.8)	41.7 (12.8)	20	22
Kim 2015	Endoscopic surgery	0.5 mcg/kg 5 min + 03-0.7 mcg/kg/h	0.5 mg/kg + 30 mcg/kg/min	62.1 (10.3)	62.9 (12.3)	29	30
Wu Y 2015	Endoscopy	1 mcg/kg 10 min + 0.5 mcg/kg/h	0.6 mg/kg + 10-20 mg bolus	40.4 (11.6)	39.0 (14.4)	33	34
Takimoto 2011	Endoscopic tumour resection	0.25 mcg/kg 5 min + 0.4 mcg/kg/h	5 mg + 3 mg/kg/h	52-80	47-79	30	30
Loh 2016	MRI	1 mcg/kg 10 min + 0.2-0.7 mcg/kg/h	TCI, 1.5 mcg/ml titrated in 0.1 mcg/ml increments, final mean dose 2.1 mcg/ml	49.1 (18.0)	45.4 (14.6)	15	15
Sriganesh 2015	Cerebral angiography	1 mcg/kg 10 min + 0.5 mcg/kg/h	1.5 mg + 1.5 mg/kg/h	49.0 (10.7)	49.0 (11.4)	30	30
Frolich 2013	Pain perception, healthy	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 0.4, 0.8, 1.2, 1.6 mcg/ml plasma cc	24.7 (4.5)	24.5 (4.6)	28	31

Reference	Type of procedure	Dose		Age (years)[a]		No. of patients	
		DEX	PRO	DEX	PRO	DEX	PRO
	volunteers						
Frolich 2011	Hemodynamic test, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 0.1, 0.2, 0.4, 0.8 mcg/ml plasma cc	21-55	21-55	20	20
Kasuya 2009	BIS and OAA/S comparison, healthy volunteers	TCI, to 0.6,1.2, 2.4 ng/ml plasma cc	TCI to 1, 2, 4 mcg/ml effect site cc	24 (4)	24 (4)	9	9

[a] Values are presented as mean (SD) or range.

Table 14. Dosing in the DEX-MDZ literature review selection - all studies

Reference	Type of procedure	Dose		Age (years)[a]		No. of patients	
		DEX	MDZ	DEX	MDZ	DEX	MDZ
Mishina 2017	Hernia repair	0.5 mcg/kg in 10 min + 0.4 mcg/kg/h	2 mg	66.5 (11.7)	65.2 (11.6)	99	97
Jo 2016	Elective surgery (knee, tibiofibular, ankle, foot) in spinal anaesthesia	1 mcg/kg in 10 min + 0.5 mcg/kg/h	0.05 mg/kg + 0.025 mg/kg/h	47.1 (15.2)	47.0 (16.2)	58	58
Peng 2016	Lumbar disc surgery	0.5 mcg/kg in 10 min + 0.5 mcg/kg/h	0.05 mg/kg + 0.05 mg/kg/h	43.1 (10.1)	44.3 (11.4)	30	30
Apan 2009	Cataract surgery	no loading dose, 0.25 mcg/kg/h	25 mcg/kg/h	65.7 (11.3)	65.8 (11.8)	30	30
Alhashemi 2006	Cataract surgery	1 mcg/kg in 10 min + 0.1-0.7 mcg/kg/h	20 mcg/kg + 0.5 mg in boluses	34-79	40-75	22	22
Fan 2013	Dental surgery	0.1 mcg/kg/min until adequate sedation + 0.2 mcg/kg/h	0.005 mg/kg/min until adequate sedation + 0.01 mg/kg/h	26 (7)	29 (9)	30	30
Cheung 2007	Dental surgery	up to 1 mcg/kg in 10 min	5 mg	25.5 (4.2)	27.7 (7.1)	30	30
Ustun 2006	Dental surgery	1 mcg/kg in 15 min	0.1 mg/kg	17-28	17-28	20	20
Liao 2012	Bronchoscopy	1 mcg/kg in 10 min + 0.5 mcg/kg/h	2 mg + 1 mg in bolus as needed	58.5 (9.1)	60.1 (8.4)	99	99
Kaya 2010	Urology - TURP in spinal anaesth	0.5 mcg/kg in 10 min	0.05 mg/kg	56.6 (8.5)	54.8 (6.4)	25	25
Takimoto 2011	Endoscopic tumour resection	0.25 mcg/kg in 5 min + 0.4 mcg/kg/h	0.1 mg/kg + 1 mg in bolus as needed	52-80	48-80	30	30

Demirarian 2007	Upper endoscopy	1 mcg/kg in 10 min + 0.2 mcg/kg/h	0.07 mg/kg	42.2 (14.4)	43.3 (13.2)	25	25
Frolich 2013	Pain perception, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 10, 20, 40, 80 ng/ml plasma cc	24.7 (4.5)	24.5 (4.6)	28	27
Frolich 2011	Hemodynamic test, healthy volunteers	TCI to 0.1, 0.2, 0.4, 0.8 ng/ml plasma cc	TCI to 10, 20, 40, 80 ng/ml plasma cc	21-55	21-55	20	20

[a] Values are presented as mean (SD) or range.

2.4.3. Discussion on clinical efficacy

There is no doubt that DEX is a sedative agent, like other alpha-2 agonists, as it is approved for the sedation of patients in the ICU setting and there is extensive clinical experience with the product. As such, the two pivotal trials do not address the question that is most relevant to this application, which is how the drug, at the proposed doses, performs in relation to standard sedation methods used for procedural sedation. In this clinical situation, the key desirable properties of a sedative agent include:

- a fast and predictable onset of action
- the ability to titrate the dose according to clinical response so that the desired level of sedation can be easily achieved and maintained
- provides a quality of sedation whereby the patient is relaxed, relieved of any anxiety, but conscious and responsive to commands
- lack of accumulation with prolonged administration (long procedures)
- does not cause substantial respiratory or cardiovascular depression

If a new sedative agent failed substantially on any of these criteria, the benefit – risk might be considered unfavourable, despite a proven greater sedative effect than placebo. A comparison with placebo in this situation is therefore largely meaningless. Unfortunately, the design of the trials, with a placebo control for the loading dose period followed by “rescue medication” with midazolam given in a way that is far from representative of normal clinical practice (very small doses given in widely spaced increments), does not allow for anything close to a direct comparison of the proposed new DEX regimen with standard of care sedation with midazolam. The placebo / midazolam group is fundamentally disadvantaged in comparison to the DEX group by the design of the trial.

However, it is possible to conclude quite a lot about the clinical utility of DEX in the proposed new indication for procedural sedation without relying heavily on the comparisons with placebo / midazolam. The overall weight of evidence is sufficient to establish that DEX, if given at a sufficient dose, is sufficiently efficacious as a sedative drug to be used for procedural sedation, at least where only a light level of sedation is required. The loading dose of 1.0 mcg/kg given over 10 minutes was superior to the 0.5 mcg/kg given over the same time and 2 mcg/kg seems likely to result in overdosage for some patients. The loading dose of 0.7 mcg/kg used in the AWAKE study was associated with a need for supplemental midazolam in half of the patients so this appears to be an insufficient dose. 1.0 mcg/kg therefore seems to be a reasonable starting point but it seems clear that

it will be insufficient for a significant proportion of patients. It is far from desirable to rely on a second agent (midazolam) to achieve sedation and it seems unimpressive that even in the high loading dose DEX group in the MAC study, half of the patients required rescue midazolam. The MAH has been asked to discuss whether dose recommendations might be revised so that adequate sedation can be achieved reliably and in an acceptable time frame with just DEX. The SmPC has been updated accordingly.

There are also issues with the maintenance dose regimen advised in the SPC (which is the same as that in the trial protocols). This posology seems to be insufficient in about half of the patients. The need for rescue midazolam in the MAC trial generally occurred late (median time 114 minutes after start of infusion). The MAH has discussed whether the upper recommended maintenance infusion rate of 1 microgram/kg/hour should be revised upwards. It is notable that the most common protocol deviation was provision of rescue MDZ prior to finalising the titration of DEX. Further clarification was provided regarding the titration procedure.

There is no rational justification for the SmPC to recommend a lower loading dose for awake fibreoptic intubation than for other types of procedural sedation. This is clearly proposed because of the AWAKE trial protocol, but it makes no sense clinically and indeed the lower loading dose in the AWAKE trial appeared to be insufficient in many patients. The separate posology for awake fibreoptic intubation has been deleted.

Further “real world” observational data might be obtained post approval to clarify dose requirements in procedural sedation, for both loading dose and maintenance.

Finally, some analgesic effect of DEX was apparent, in line with the known pharmacology of DEX. This could be a significant advantage in patients for whom opioids are problematic, either for safety reasons (respiratory depression) or because the subject is taking an opioid antagonist (e.g. naltrexone for drug / alcohol misuse). However in most patients undergoing procedural sedation it is routine and very easy to give suitable analgesia to cover painful procedures so an opioid sparing effect is not of great value.

2.4.4. Conclusions on clinical efficacy

It can be concluded that DEX is efficacious as a sedative drug for procedural sedation.

2.5. Clinical safety

Introduction

The safety profile of dexmedetomidine for the sedation of critically ill patients in the ICU was established in the original MAA and has been supplemented by the ongoing post-marketing use. Based on the figures presented in PSUR AR (EMEA/H/C/PSUSA/00000998/201703) covering the period 16 March 2016 to 15 March 2017, the cumulative exposure to DEX products, Dexdor and Precedex, during Dec 1999 – Feb 2017 can be estimated to exceed 12 million patient days. The safety documentation in this variation application is focused on the proposed new indication only. Safety information in the initial MAA is to a large extent applicable to the new indication. However there are some important differences between the existing and proposed indications that require a different safety perspective. In particular, CNS, cardiovascular and respiratory depression that persist after the period of sedative

drug administration are much more important potential safety issues in the procedural sedation setting than in the ICU setting.

The MAC and AWAKE studies were included in the initial 2010 MAA but only for the purpose of completeness of documentation and providing supporting information. The MAH has now presented the safety data from those studies in detail. Most safety data are taken directly from the study reports, however the MAH has performed a number of post-hoc additional exploratory analyses in order to more clearly present the study data in the Clinical Summary of Safety.

As an established drug being used in a similar way to its existing EU approval, no new non-clinical studies have been performed. While procedural sedation does raise some different questions in relation to safety than the ICU submission, there are none for which further non-clinical work would have been of significant value.

There are many studies published detailing the use of dexmedetomidine for procedural sedation but in size, robustness and completeness of safety data collection, the MAC and AWAKE studies are clearly pre-eminent. The MAH has provided full study data for both studies. It is appropriate that the evaluation of dexmedetomidine safety in procedural sedation should be based primarily on the MAC and AWAKE studies. Published studies complement the results from MAC and AWAKE studies and address relevant safety information outside the scope of those studies. The detail in which safety data are presented in published studies is frequently rather limited and thus it is to be expected that some arguments and conclusions presented based on original clinical trials documentation may differ from a MAA based entirely on published literature data, for example for Ever Pharma dexmedetomidine product recently approved in many EU member states.

The MAC and AWAKE studies both included patients with a broad range of comorbidities, including severe systemic disease, and monitored them closely for both cardiovascular and respiratory function during and after the study drug infusion. AE follow-up was for 24 hours after the end of study drug infusion and for serious adverse events (SAEs) the period was 30 days. Other safety parameters, such as safety laboratory and 12-lead electrocardiogram (ECG), were monitored to a degree appropriate to a drug already approved and used extensively for longer duration in critically ill patients.

The method of dosing is an important focus in this application. The use of a loading dose (commonly 1 mcg/kg infused over 10 minutes) was already long-established in non-EU countries and so was not specifically evaluated in the reports for the MAC and AWAKE studies. For the sedation of patients in the ICU, it is not normally necessary to achieve a rapid effect with dexmedetomidine because patients are commonly already sedated on another drug or under general anaesthesia. For procedural sedation a rapid onset of effect will almost always be needed, necessitating use of a loading dose of dexmedetomidine. The Applicant has thus prepared some additional analyses to explore the safety implications of the use of loading dose in this population of patients.

Patient exposure

The safety database comprises the complete study data of the individual MAC and AWAKE studies and a pooled database comprising baseline, exposure and AE data from the 2 studies. The study designs mean that there are some differences in the AE collection period (the study drug infusion was longer in the MAC study and a distinct PACU period was defined) and in the nature of the subjects enrolled that might be expected to influence the study results. Therefore the pooled data only provide supportive evidence to the individual studies. The same pooled database was presented in the Dexdor 2010 MAA

although in that application the MAC and AWAKE studies were combined with other non-ICU studies in many analyses. In this application all analyses of pooled data comprise only these 2 studies. With only 2 studies, the contribution of the pooled analyses to understanding the data is quite limited. Other safety parameters have not been pooled: differences in study design and data collection schedules and the limited value of pooling only 2 studies suggest such an attempt would have been of little value.

The number of subjects included in the safety database is summarised in Table 5. The total of 318 subjects treated with DEX in this specific indication is sufficient to evaluate any safety issues peculiar to the use of DEX for procedural sedation, especially when supported by a large number of published studies.

Table 15. Number of subjects in the safety database

DEX loading dose	DEX 0.5 μg/kg	DEX 1 μg/kg	DEX total	PBO	Total
Study					
2005-005 (MAC)	134	129	263	63	326
2005-006 (AWAKE)	-	55	55	50	105
Pooled database	134	184	318	113	431

The baseline characteristics of the patients in the phase III safety database are summarised in Table 6. The subjects were well matched between treatment groups within each study and the studies enrolled quite similar populations. Overall this was a predominantly middle-aged Caucasian population with significant systemic co-morbidity (ASA II-III), with some slight over-representation of males, which is probably similar to what can be expected in Europe. A meaningful number of patients with morbidity that is a constant threat to life (ASA IV) were also included. Close to 30% of subjects were over 65 years old. Many subjects were receiving extensive concomitant medications, being especially treatments for hypertension (renin-angiotensin-system blockers, beta-blockers), diabetes and lipid disorders. In the AWAKE study 49% of subjects were being treated for hypertension or cardiovascular disease (36% of placebo subjects) and 25.5% were diabetic (placebo 18.8%). This very broad mix of subjects with relatively high level of comorbidity represents a good test of the safety of dexmedetomidine for clinical use during procedural sedation: in many cases combined local/regional anaesthesia with sedation is chosen in patients at higher risk from general anaesthesia.

Table 16. Demographic and baseline characteristics of subjects in the procedural sedation safety database

Variable		All DEX (N=318)	PLACEBO (N=113)
		n (%)	n (%)
Age (years)	N	318	113
	Mean	54.9	53.8
	SD	16.2	16.1
	Min	18	19
	Median	55.5	56.0
	Max	93	80
Age category	≤ 65 years	230 (72.3)	83 (73.5)
	> 65-75 years	59 (18.6)	22 (19.5)

Variable		All DEX (N=318)	PLACEBO (N=113)
		n (%)	n (%)
	> 75 years	29 (9.1)	8 (7.1)
Sex	Female	152 (47.8)	41 (36.3)
	Male	166 (52.2)	72 (63.7)
Race	Caucasian	194 (61.0)	76 (67.3)
	Black	63 (19.8)	19 (16.8)
	Asian	4 (1.3)	1 (0.9)
	Hispanic	56 (17.6)	17 (15.0)
	Other	1 (0.3)	0
ASA classification, n (%)	ASA I	36 (11.3)	9 (8.0)
	ASA II	143 (45.0)	50 (44.2)
	ASA III	116 (36.5)	46 (40.7)
	ASA IV	23 (7.2)	8 (7.1)

Source: m5.3.5.3 Additional analyses for studies supporting procedural sedation, Table 14.1.2

The medical entry criteria between the 2 studies were closely aligned and relevant to the target population as well as the existing Dexdor SmPC. Three exclusions are worth noting:

- Subjects requiring a spinal or epidural were excluded. Major regional blocks such as spinal or epidural are associated with hypotension as a result of sympathetic blockade leading to vasodilation in the limbs. However this is a clinical situation in which procedural sedation is frequently used and will be reviewed later.
- Subjects potentially less able to tolerate hypotensive or bradycardic effects of dexmedetomidine, such as acute myocardial ischaemia, unstable angina, complete heart block, bradycardia or hypotension. There are comparable warnings (and contraindication in the case of heart block) in the EU SmPC for Dexdor and these seem appropriate to use in procedural sedation too.
- Subjects with a CNS disease involving raised intracranial pressure or cerebrospinal fluid leak were excluded. However such patients are unlikely to be considered suitable candidates for procedural sedation, and so the impact on the data can be considered minimal.

The patients were all treated in hospital in the operating/anaesthesia room prior to surgery and with an anaesthetist in attendance, who was responsible for managing the sedation and for the identification, management and recording of AEs. This is a key element in the reliability of the safety data.

The population in the MAC and AWAKE studies are representative of the target patient population and so support the safety assessment of dexmedetomidine in procedural sedation in adults.

2.5.1. Patient exposure

In the AWAKE study DEX-treated subjects received a 1 mcg/kg loading dose administered over 10 minutes, followed by a continuous infusion at 0.7 mcg/kg/h until successful completion of the fibreoptic intubation. In the MAC study DEX -treated patients were randomised to receive a loading dose of either 0.5 or 1 mcg/kg over 10 minutes, followed by a continuous infusion starting at 0.6 mcg/kg/h and titrated as required within the range 0.2-1 mcg/kg/h. These loading doses are in line with those

used in studies reported in the literature. The upper limit of maintenance infusion rates is lower than that approved for ICU sedation in the EU (1.4 micrograms/kg/h) and reflects the lower doses approved in the USA. Most published studies of DEX in procedural sedation have employed a similar dose scheme. In total 134 and 184 subjects received loading doses of 0.5 mcg/kg and 1 mcg/kg dexmedetomidine respectively in the MAC and AWAKE studies.

The duration and total dose of exposure to dexmedetomidine in the MAC and AWAKE studies is summarised in Table 7, along with the mean maintenance dose administered in the MAC study according to type of surgical procedure. More than 75% of subjects received dexmedetomidine for less than 2 hours and most subjects in clinical practice would not exceed this duration of treatment. The maximum duration in excess of 6 hours in one patient is unusual and likely to be a rare event in practice. The mean maintenance dose was in the range 0.49-0.7 mcg/kg/h in the MAC study and there is a suggestion that the mean dose used in some procedures (notably ophthalmology) may be lower, perhaps linked to the level of comfort or stimulation involved in the surgery. Low doses of dexmedetomidine (0.5 mcg/kg loading followed by 0.2 mcg/kg/h maintenance) have been used successfully in ophthalmic surgery (Abdalla et a 2006). It is of note though at least 1 patient in each procedure type in the MAC study received the maximum permitted maintenance dose of dexmedetomidine for the proposed indication.

Table 17. Exposure to study drug in the MAC and AWAKE studies

Variable	MAC study			AWAKE study	
	DEX 0.5 mcg/kg N = 134	DEX 1 mcg/kg N = 129	PBO N = 63	DEX 1 mcg/kg N = 55	PBO N = 50
Duration of study drug exposure (minutes)					
Mean (SD)	97.0 (52.51)	102.3 (59.66)	105.6 (47.36)	37.7 (15.4)	41.5 (18.4)
Median	82.0	82.0	98.0	35.0	37.0
Range	10.0 – 315.0	6.0 – 370.0	43.0 – 296.0	20 – 92	23 – 120
Total dose of study drug received (mcg/kg)					
Mean (SD)	1.4 (0.67)	1.9 (0.79)	NA	1.32 (0.179)	NA
Median	1.2	1.7	NA	1.285	NA
Range	0.5 – 4.2	0.6 – 6.7	NA	1.12 – 1.96	NA
Duration of fiberoptic intubation (minutes) (AWAKE study only)					
N	-	-	-	53	49
Mean (SD)	-	-	-	5.2 (6.1)	3.7 (4.8)
Median	-	-	-	3.0	2.0
Range	-	-	-	0 – 34	0 – 26

Mean maintenance doses used in the MAC study are shown by procedure type in Table 18. Analysis of the maintenance dose indicated that older patients were maintained on similar doses to younger patients, although some group sizes were very small.

Table 18. Maintenance doses of DEX by procedure type and age in MAC study

Surgery/procedure type		Maintenance dose (mcg/kg/h)			
		N	Mean (SD)	Median	Range
Pooled Type 1	Orthopaedic	77	0.70 (0.21)	0.73	0.29 - 1.0
	≤ 65 years	71	0.70 (0.21)	0.73	0.29 - 1.0
	> 65-75 years	5	0.64 (0.25)	0.67	0.38 - 0.91
	> 75 years	1	0.79 (-)	0.79	-
Pooled Type 2	Ophthalmic	69	0.49 (0.23)	0.53	0.04 - 0.97
	≤ 65 years	32	0.59 (0.22)	0.58	0.18 - 0.97
	> 65-75 years	23	0.41 (0.19)	0.38	0.14 - 0.76

	> 75 years	14	0.42 (0.24)	0.43	0.04 - 0.72
Pooled Type 3	Breast biopsy, excision of lesion, plastics	71	0.70 (0.18)	0.71	0.24 - 0.99
	≤ 65 years	55	0.71 (0.18)	0.72	0.32 - 0.99
	> 65-75 years	11	0.69 (0.20)	0.71	0.34 - 0.95
	> 75 years	5	0.57 (0.22)	0.60	0.24 - 0.87
Pooled Type 4	AV fistula, vascular stent, other	44	0.55 (0.19)	0.56	0.23 - 0.99
	≤ 65 years	28	0.53 (0.20)	0.52	0.23 - 0.95
	> 65-75 years	8	0.68 (0.19)	0.601	0.47 - 0.99
	> 75 years	8	0.51 (0.12)	0.533	0.26 - 0.61

Shows mean infusion rate of DEX after completion of the loading dose

In the AWAKE study all patients received the same maintenance dose of 0.6 mcg/kg/h after completing the loading dose.

Combining the MAC and AWAKE studies, the mean duration of exposure to DEX was 1.5 hours and in 78% and 92.8% of patients the duration was less than 2 and 3 hours respectively. The longest exposure exceeded 6 hours in a single patient.

Table 19. Duration of DEX exposure in pooled MAC and AWAKE studies

Variable		All DEX (N = 318)
Duration of infusion (hours)	N	318
	Mean	1.5
	SD	0.9
	Min	0
	Median	1.3
	Max	6
Duration of infusion category (hours)	≤ 1	111 (34.9)
	≤ 2	137 (43.1)
	≤ 3	47 (14.8)
	≤ 4	17 (5.3)
	≤ 5	4 (1.3)
	≤ 6	1 (0.3)
	≤ 7	1 (0.3)
Total patient days		19.6
Total patient days by duration of infusion	≤ 1 H	3.1
	≤ 2 H	8.0
	≤ 3 H	4.9
	≤ 4 H	2.4
	≤ 5 H	0.8
	≤ 6 H	0.2
	≤ 7 H	0.3

All patients received a loading dose (0.5 or 1.0 mcg/kg) of DEX over 10 minutes, making the dose per patient somewhat higher than the maintenance dose specified in the protocols. The shorter the duration of maintenance infusion the larger will be the impact of the loading dose and the maximum dose/hour of 6 mcg/kg/h is equivalent to stopping the infusion immediately after a 1.0 mcg/kg loading dose.

Table 20. Extent of DEX exposure in pooled MAC and AWAKE studies

Variable		All DEX (N = 318)
Total cumulative dose (mcg/kg)	N	318
	Mean	1.6
	SD	0.7
	Min	1
	Median	1.4
	Max	7
Dose per hour (mcg/kg/h)	N	318
	Mean	1.3
	SD	0.7
	Min	0
	Median	1.2
	Max	6
Dose per hour category, n (%)	≤ 0.7 mcg/kg/h	39 (12.3)
	> 0.7-1.1 mcg/kg/h	97 (30.5)
	> 1.1 mcg/kg/h	182 (57.2)
Total patient days by dose	≤ 0.7 mcg/kg/h	3.9
	> 0.7-1.1 mcg/kg/h	7.8
	> 1.1 mcg/kg/h	7.9

Elderly patients and patients with relevant comorbidity

Table 21. Demographic characteristics in the MAC and AWAKE studies

Variable	MAC study			AWAKE study	
	DEX 0.5 mcg/kg N = 134	DEX 1 mcg/kg N = 129	PBO N = 63	DEX 1 mcg/kg N = 55	PBO N = 50
Age, years					
Mean (SD)	56.8 (16.51)	53.8 (16.47)	55.3 (16.69)	52.6 (14.14)	51.9 (15.27)
Range	18 – 93	19 – 88	20 – 80	21 – 78	19 – 77
Gender, n (%)					
Male	68 (50.7)	65 (50.4)	36 (57.1)	33 (60.0%)	36 (72.0%)
Female	66 (49.3)	64 (49.6)	27 (42.9)	22 (40.0%)	14 (28.0%)
Ethnic origin, n (%)					
Caucasian	91 (67.9)	74 (57.4)	39 (61.9)	29 (52.7%)	37 (74.0%)
Black	23 (17.2)	30 (23.3)	14 (22.2)	10 (18.2%)	5 (10.0%)
Asian	1 (0.7)	3 (2.3)	1 (1.6)	0	0
Hispanic	18 (13.4)	22 (17.1)	9 (14.3)	16 (29.1%)	8 (16.0%)
Other	1 (0.7)	0	0	0	0
Weight, kg					
Mean (SD)	84.9 (21.02)	83.0 (19.34)	86.9 (21.75)	93.51 (29.81)	94.52 (23.89)
Range	51 – 167	45 – 155	48 – 136	46.7 – 203.2	44.0 – 147.7
Height, cm					
Mean (SD)	-	-	-	170.25 (10.86)	174.42 (13.63)
Range	-	-	-	150.0 – 196.9	145.0 – 223.5
ASA classification, n (%)					
ASA I	13 (9.7)	22 (17.1)	6 (9.5)	1 (1.8)	3 (6.0)
ASA II	63 (47.0)	57 (44.2)	32 (50.8)	23 (41.8)	18 (36.0)
ASA III	51 (38.1)	40 (31.0)	20 (31.7)	25 (45.5)	26 (52.0)
ASA IV	7 (5.2)	10 (7.8)	5 (7.9)	6 (10.9)	3 (6.0)

In both studies at least 75% of patients were ASA II or III, meaning that they had systemic disease. In the AWAKE study this was more often severe (ASA III, 45.5 – 52.0%) than in MAC (ASA III, 31.0 – 38.1%). In total 31 patients (23 on DEX) had a severe systemic disease considered a constant threat to life (ASA IV). In MAC, the majority of patients were using at least 1 medication before the start of study drug infusion. Among the most common medications used prior to start of study drug were acetylsalicylic acid (22.4%, 20.9%, 23.8%), metoprolol (9.0%, 4.7%, 3.2%), and hydrochlorothiazide (8.2%, 9.3%, 7.9%), in the DEX 0.5 mcg/kg group, DEX 1 mcg/kg group, and PBO group, respectively. In AWAKE, of patients receiving DEX, 49% (27/55) were being treated for hypertension or cardiovascular disease. Differences in cardiovascular medications between DEX and PBO groups respectively included beta-blockers (32.7 vs. 14.0%), calcium channel blockers (12.7 vs. 6.0%) and diuretics (18.2 vs. 10.0%). A history of diabetes was reported for 25.5% and 18% of DEX and PBO patients, respectively.

Adverse events

In both studies, the desired level of sedation was achieved in nearly all patients with few symptomatic adverse effects. In total 83.6% of dexmedetomidine-treated subjects experienced an AE either during the infusion, PACU or the 24 hour follow-up period compared to 71.7% placebo subjects and these AEs were more likely to be deemed treatment-related by the investigators.

Fewer than 2% of events in either group were recorded as severe. The reporting of AEs was quite consistent between the two phase III studies with very similar overall AE incidence during study drug infusion between the 2 placebo groups (58.7% vs. 58.0%) and DEX 1 mcg/kg loading dose groups (68.2% vs. 63.6%) in MAC and AWAKE studies respectively. The incidence of AEs was highest in the DEX 0.5 mcg/kg loading dose group (79.9%) during the study drug infusion period in the MAC study, with 56% of subjects having a treatment-related AE. The overall incidence of AEs during the 24 hour follow-up was somewhat lower than during the infusion and was similar in all treatment groups.

Overview of adverse events in pooled phase III studies

Category	All DEX (N = 318)	PBO (N = 113)
Number of patients who had AEs, n (%)	266 (83.6)	81 (71.7)
Number of AEs, n	531	181
Number of patients who had treatment related AEs, n (%)	169 (53.1)	32 (28.3)
Number of treatment related AEs, n	293	41
Number of patients who had moderate or severe AEs, n (%)	71 (22.3)	23 (20.4)
Number of moderate or severe AEs, n	107	32
Number of patients who had SAEs, n (%)	5 (1.6)	3 (2.7)
Number of SAEs, n	6	3
Number of patients who had AEs leading to discontinuation of study treatment[a], n (%)	6 (1.9)	1 (0.9)

[a] Discontinuations include patients who had AE marked as the primary, secondary or third reason for discontinuation

Source: m5.3.5.3 Additional analyses for procedural sedation, Table 14.3.1.1

All AEs reported during the study drug infusion in more than one subject in either the MAC or AWAKE study are shown in Table 9 and AEs during the 24 hour follow-up are in Table 10.

Qualitatively the reported AEs reflect the known effects of dexmedetomidine and what could be expected from performing such procedures in the studied populations of subjects. Given the preponderance of ASA II-III patients an entirely uneventful perioperative period was not to be expected.

During study drug infusion, the great majority of AEs reported related to protocol-defined cardiovascular events (especially hypotension) and respiratory depression. Hypotension (defined as SBP < 80 mmHg OR >30% lower than pre-study drug infusion values OR DBP < 50 mmHg) was reported in 47.8%, 31.8% and 27.0% of DEX 0.5 mcg/kg, DEX 1 mcg/kg and placebo subjects respectively in the MAC study while hypertension incidence was similar in all treatment groups occurring in 8.2%, 8.5% and 12.7% of DEX 0.5 mcg/kg, DEX 1 mcg/kg and placebo subjects respectively. Protocol-defined bradycardia was reported in 13.2% DEX 1 mcg/kg patients in the MAC study. In the AWAKE study hypertension was overall the most frequently reported AE, in 23.6% and 28.0% of DEX and placebo subjects respectively. Still, hypotension was the most common AE on DEX in 27.3% subjects compared to 6.0% of placebo subjects.

Protocol-defined respiratory depression (RR < 8 bpm OR > 25% decrease from baseline) was a common finding but not different between DEX and placebo groups in either study. In the MAC study it occurred in between 33.3-37.3% subjects and in 14-16.4% subjects in AWAKE. In only a small number of subjects this appeared to be associated with an effect on oxygen saturation.

AEs apart from these cardiovascular and respiratory events were relatively few and without consistent differences between treatment groups during study drug infusion. Indeed most AE terms were reported for only a single patient. Single cases of ventricular tachycardia, palpitations and extrasystoles were reported on DEX 1 mcg/kg in the MAC study. The case of ventricular tachycardia was considered related to underlying coronary artery disease by the investigator: it occurred more than 1 hour after the start of DEX, lasted for 12 beats and no action was taken.

Table 22. Adverse events reported during dexmedetomidine infusion in >2 subjects in either MAC or AWAKE studies

	MAC study			AWAKE study	
Preferred term	DEX 0.5mcg/kg N=134	DEX 1.0mcg/kg N=129	Placebo N=63	DEX 1.0mcg/kg N=55	Placebo N=50
	No. (%) of subjects				
Any adverse event	**107 (79.9)**	**88 (68.2)**	**37 (58.7)**	**35 (63.6)**	**29 (58.0)**
Hypotension	64 (47.8)	41 (31.8)	17 (27.0)	15 (27.3)	3 (6.0)
Respiratory depression	50 (37.3)	44 (34.1)	21 (33.3)	9 (16.4)	7 (14.0)
Bradycardia	12 (9.0)	17 (13.2)	3 (4.8)	4 (7.3)	0
Hypertension	11 (8.2)	11 (8.5)	8 (12.7)	13 (23.6)	14 (28.0)
Tachycardia	4 (3.0)	7 (5.4)	7 (11.1)	2 (3.6)	0
Bradypnoea	0	0	0	5 (9.1)	5 (10.0)
Dry mouth	4 (3.0)	4 (3.1)	0	0	0
Headache	2 (1.5)	1 (0.8)	0	0	1 (2.0)
Dry throat	2 (1.5)	0	0	0	0

Hypoxia	2 (1.5)	1 (0.8)	2 (3.2)	4 (7.3)	1 (2.0)
Diastolic hypertension	2 (1.5)	0	0	0	1 (2.0)

Source: 2005-005 CSR, Table 14.3.1.4.1 and 2005-006 CSR Table 14.3.1.3.1

Adverse events reported during dexmedetomidine infusion in MAC study

Preferred Term	DEX 0.5 mcg/kg N = 134	DEX 1 mcg/kg N = 129	PBO N = 63
	n (%) of patients		
Any adverse events	**107 (79.9)**	**88 (68.2)**	**37 (58.7)**
Hypotension	64 (47.8)	41 (31.8)	17 (27.0)
Respiratory depression	50 (37.3)	44 (34.1)	21 (33.3)
Bradycardia	12 (9.0)	17 (13.2)	3 (4.8)
Hypertension	11 (8.2)	11 (8.5)	8 (12.7)
Tachycardia	4 (3.0)	7 (5.4)	7 (11.1)
Dry mouth	4 (3.0)	4 (3.1)	0
Headache	2 (1.5)	1 (0.8)	0
Dry throat	2 (1.5)	0	0
Hypoxia	2 (1.5)	1 (0.8)	2 (3.2)
Diastolic hypertension	2 (1.5)	0	0
Hyperhidrosis	1 (0.7)	0	0
Pruritus	1 (0.7)	0	0
Urticaria	1 (0.7)	0	0
Dizziness	1 (0.7)	0	0
Somnolence	1 (0.7)	0	0
Dyspnoea	1 (0.7)	0	0
Extrasystoles	0	1 (0.8)	0
Palpitations	0	1 (0.8)	0
Ventricular tachycardia	0	1 (0.8)	0
Agitation	0	1 (0.8)	0
Delirium	0	1 (0.8)	0
Dysphoria	0	1 (0.8)	0
Restlessness	0	1 (0.8)	0
Obstructive airways disorder	0	1 (0.8)	0
Tremor	0	0	1 (1.6)

Source: 2005-005 CSR, Table 14.3.1.4.1

Adverse events reported during dexmedetomidine infusion in AWAKE study

Preferred Term	DEX 1 mcg/kg N = 55	PBO N = 50
	n (%) of patients	

Any adverse events	**35 (63.6)**	**29 (58.0)**
Hypertension	13 (23.6)	14 (28.0)
Hypotension	15 (27.3)	3 (6.0)
Respiratory depression	9 (16.4)	7 (14.0)
Tachycardia	4 (7.3)	12 (24.0)
Bradypnoea	5 (9.1)	5 (10.0)
Hypoxia	4 (7.3)	1 (2.0)
Bradycardia	4 (7.3)	0
Tachypnoea	2 (3.6)	0
Atrioventricular block first degree	1 (1.8)	0
Haematuria	1 (1.8)	0
Agitation	0	1 (2.0)
Diastolic hypertension	0	1 (2.0)
Headache	0	1 (2.0)
Intubation complication	0	1 (2.0)
Neck pain	0	1 (2.0)
Pharyngolaryngeal pain	0	1 (2.0)
Systolic hypertension	0	1 (2.0)

Source: study 2005-006 Table 14.3.1.3.1

Table 23. Adverse events reported during 24 hour follow-up in >2 subjects in either MAC or AWAKE studies

	MAC study			AWAKE study	
Preferred term	DEX 0.5mcg/kg N=134	DEX 1.0mcg/kg N=129	Placebo N=63	DEX 1.0mcg/kg N=55	Placebo N=50
	No. (%) of subjects				
Any adverse event	**31 (23.1)**	**35 (27.1)**	**16 (25.4)**	**18 (32.7)**	**15 (30.0)**
Hypotension	11 (8.2)	21 (16.3)	1 (1.6)	7 (12.7)	11 (22.0)
Respiratory depression	6 (4.5)	7 (5.4)	5 (7.9)	0	0
Bradycardia	4 (3.0)	5 (3.9)	0	1 (1.8)	1 (2.0)
Hypertension	2 (1.5)	0	6 (9.5)	4 (7.3)	4 (8.0)
Nausea	4 (3.0)	1 (0.8)	1 (1.6)	3 (5.5)	1 (2.0)
Tachycardia	1 (0.7)	0	0	1 (1.8)	1 (2.0)
Headache	0	2 (1.6)	1 (1.6)	0	0
Pruritus	0	1 (0.8)	2 (3.2)	0	0
Anxiety	1 (0.7)	0	1 (1.6)	0	0
Dizziness	0	1 (0.8)	1 (1.6)	0	0
Post procedural nausea	0	1 (0.8)	1 (1.6)	0	0
Syncope vasovagal	1 (0.7)	1 (0.8)	0	0	0
Vomiting	1 (0.7)	0	1 (1.6)	0	0
Procedural pain	0	0	0	2 (3.6)	0
Pharyngolaryngeal pain	0	0	0	1 (1.8)	1 (2.0)

Source: 2005-005 CSR Table 14.3.1.4.3 and 2005-006 CSR Table 14.3.1.3.2

AEs reported in PACU in MAC study

Preferred Term	DEX 0.5 mcg/kg N = 134	DEX 1 mcg/kg N = 129	PBO N = 63
	n (%) of patients		
Any adverse events	**17 (12.7)**	**18 (14.0)**	**8 (12.7)**
Hypotension	9 (6.7)	14 (10.9)	3 (4.8)
Bradycardia	3 (2.2)	4 (3.1)	0
Respiratory depression	2 (1.5)	2 (1.6)	4 (6.3)
Nausea	2 (1.5)	0	0
Hypertension	1 (0.7)	0	1 (1.6)
Hypoglycaemia	1 (0.7)	0	0
Atrioventricular block first degree	0	1 (0.8)	0
Cardiac disorder	0	1 (0.8)	0
Muscle twitching	0	1 (0.8)	0
Procedural pain	0	0	1 (1.6)
Hiccups	0	0	1 (1.6)
Obstructive airways disorder	0	0	1 (1.6)
Pulmonary oedema	0	0	1 (1.6)

Source: 2005-005 CSR, Table 14.3.1.4.2

In the MAC study, the AEs reported during the time in PACU were somewhat comparable between treatment groups, with insufficient events reported to make meaningful comparisons.

The most frequent AE during the follow-up period remained hypotension. Hypotension was recorded in 16.3% of DEX 1mcg/kg subjects during the 24 hour follow-up in the MAC study, compared to 8.2% of DEX 0.5 mcg/kg and 1.6% of placebo subjects respectively. Several cases of bradycardia also occurred during this period in both DEX groups but not placebo. There was no difference in respiratory depression between the groups during this time. Subjects on placebo appeared more likely to suffer hypertension during follow-up (9.5% vs. 1.5% on DEX 0.5 mcg/kg and no subjects on DEX 1 mcg/kg).

One patient (DEX 1 mcg/kg) developed a septal myocardial infarction during the follow-up period which was described as mild and for which no action was taken. The patient had many predisposing characteristics including existing ischaemic heart disease, extensive peripheral vascular disease and diabetes. The Dexdor SmPC advises caution in patients with such a history.

Serious adverse event / deaths / other significant events

No SAEs occurred during the period of study drug infusion in either study. SAEs at other times during / after the trial (3 DEX, 5 MDZ/FEN) were in line with expectations for the patients and procedures studied. All of these SAE reports were considered unrelated by the investigators. The narratives for the SAEs support these conclusions although one SAE of hypotension starting 51 minutes after completion of dexmedetomidine infusion and lasting 55 minutes seems possibly treatment related. There were no deaths in either study.

Discontinuation due to adverse events

5 patients in the MAC study discontinued the study drug due to an AE; 3 of these patients were in the dexmedetomidine 1 mcg/kg loading dose group, 1 patient was in the dexmedetomidine 0.5 mcg/kg loading dose group, and one patient was in the placebo group. In the AWAKE study one patient in the dexmedetomidine group and one patient in placebo group discontinued due to an AE. The following table shows the AEs leading to drug discontinuation in the pooled data for the phase III studies MAC & AWAKE.

AEs leading to discontinuation of study drug in pooled phase III studies

System Organ Class Preferred Term	All DEX (N = 318)	PBO (N = 113)
	Patients n (%) Events n	
Cardiac disorders		
Total	2 (0.6) 2	0
Atrioventricular block first degree[a]	1 (0.3) 1	0
Bradycardia	1 (0.3) 1	0
General disorders and administration site conditions		
Total	1 (0.3) 1	0
Infusion site reaction	1 (0.3) 1	0
Nervous system disorders		
Total	0	1 (0.9) 1
Tremor	0	1 (0.9) 1
Psychiatric disorders		
Total	1 (0.3) 2	1 (0.9) 1
Agitation	1 (0.3) 1	1 (0.9) 1
Restlessness	1 (0.3) 1	0
Vascular disorders		
Total	1 (0.3) 1	0
Hypotension	1 (0.3) 1	0

[a] for one patient in AWAKE study for the AE 'Atrioventricular block first degree' action taken with study treatment was reported as 'study drug discontinued', but 'worsening bradycardia" was also entered as "Reason for study drug discontinuation", and as a reason for discontinuation in the 2005-006 study narrative

2.5.2. Cardiovascular effects

The cardiovascular effects of DEX, most notably bradycardia and hypotension, are well known and were extensively reviewed during the 2010 MAA. Central alpha-2 agonism leads to slowing heart rate and peripheral vasodilatation, whereas peripheral actions (at higher DEX concentrations) include vasoconstriction and slowing heart rate. The most prominent adverse effects of DEX during use in the ICU are bradycardia and hypotension, both. At high concentrations DEX may initially cause hypertension, an effect previously noted related to loading dose administration during the early ICU studies. In the absence of a loading dose, hypertension was not seen as a common effect of DEX in the ICU. At the same time, inadequate sedation during procedures may lead to pain, discomfort and sympathetic stimulation, resulting in hypertension and tachycardia.

The discussion below addresses these effects in the context of procedural sedation only, where they will be key safety issues, rather more so than in the highly controlled ICU setting.

Both MAC and AWAKE studies had the detection, management and reporting of cardiovascular adverse effects as key safety objectives. To that end the protocols contained identical pre-defined thresholds for reporting changes in blood pressure and heart rate as AEs (Table below), regardless of whether the individual change was considered of clinical relevance or required treatment. Thresholds were also established for respiratory rate and peripheral oxygen saturation (SpO2) that were similar in both studies. The impact of these thresholds on the interpretation of the AE data generated will be discussed.

Vital signs thresholds applied in MAC and AWAKE studies

Adverse event	Vital sign criteria for AE
Hypertension	SBP > 180 mmHg OR ≥ 30% higher than pre-study drug infusion values OR DBP >100 mmHg
Hypotension	SBP < 80 mmHg OR ≤30% lower than pre-study drug infusion values OR DBP < 50 mmHg
Bradycardia	HR < 40 bpm OR ≤ 30% lower than pre-study drug infusion values
Tachycardia	HR > 120 bpm OR ≥ 30% higher than pre-study drug infusion values
Respiratory depression	RR < 8 bpm OR > 25% decrease from baseline
Hypoxia	SpO_2 < 90% (85% in AWAKE) OR 10% decrease from baseline

Changes in vital signs are summarised in Table 11 for the MAC study. As expected there was a significant reduction in blood pressure (mainly systolic) in both DEX dose groups (SBP mean -18.2 mmHg vs. -11.6 mmHg during study drug infusion in DEX 0.5 mcg/kg and DEX 1 mcg/kg groups respectively) that continued into the PACU period. The reduction was greater on the lower DEX dose, although no formal statistical comparisons between DEX groups were performed. Such changes started during the loading dose, although most change occurred after that time (Figure 1). The blood pressure reduction was associated with reduced heart rate that was similar in both dose groups. Similar effects have been demonstrated previously in many settings. Xu et al (2016) found mean SBP to be 10 mmHg lower at the end of a loading dose infusion of 1 mcg/kg, very similar to the change recorded on remifentanil in the same study, along with mean heart rate that was 7 bpm lower than mean baseline.

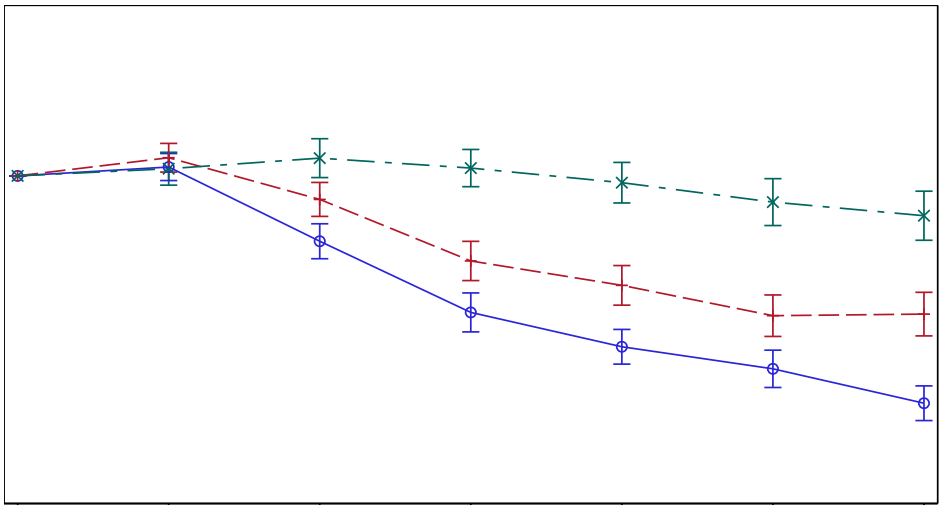
Table 24. Summary of vital signs changes in the MAC study

	DEX 0.5 mcg/kg N=134		DEX 1.0 mcg/kg N=129		Placebo N=63	
	Value (SD)	Change[a] (SD)	Value (SD)	Change[a] (SD)	Value (SD)	Change[a] (SD)
Baseline						
SBP (mmHg)	137.1 (21.63)	–	134.4 (21.13)	–	138.9 (23.06)	-
DBP (mmHg)	76.8 (11.18)	–	76.9 (12.64)	–	77.1 (13.10)	–
HR (bpm)	70.4 (10.53)	–	70.2 (10.16)	–	71.6 (11.23)	–
During study drug infusion						
SBP (mmHg)	118.9 (19.05)	*-18.2 (16.40)*	122.7 (20.20)	*-11.6 (18.48)*	132.5 (21.17)	*-6.3 (13.30)*
DBP (mmHg)	66.1 (10.61)	*-10.7 (8.73)*	68.8 (11.48)	*-8.0 (11.07)*	71.6 (14.00)	*-5.5 (7.45)*

	DEX 0.5 mcg/kg N=134		DEX 1.0 mcg/kg N=129		Placebo N=63	
	Value (SD)	Change[a] (SD)	Value (SD)	Change[a] (SD)	Value (SD)	Change[a] (SD)
HR (bpm)	64.9 (9.35)	*–5.5 (6.87)*	63.3 (8.33)	*–6.9 (8.50)*	73.5 (12.57)	*1.9 (7.68)*
During PACU						
SBP (mmHg)	109.6 (20.22)	*-27.4 (20.94)*	109.7 (19.41)	*-24.7 (19.59)*	130.8 (20.17)	*-8.2 (18.04)*
DBP (mmHg)	62.0 (10.29)	*-14.8 (10.95)*	63.0 (11.42)	*-13.9 (13.36)*	73.6 (13.32)	*-3.5 (12.04)*
HR (bpm)	62.2 (9.47)	*–8.2 (8.06)*	62.0 (8.98)	*–8.2 (9.22)*	72.8 (11.68)	*0.9 (8.55)*

[a] Change from baseline. Source: 2005-005 CSR Tables 14.3.6.1.1, 14.3.6.2.1, 14.3.6.3.1 and Appendix 16.2.10

Figure 2. Systolic blood pressure change from baseline during the first 30 minutes of dosing in the MAC study



Source: m5.3.5.3 Additional analyses for procedural sedation, Figure 1

Blood pressure and heart rate changes were less marked in the AWAKE study, perhaps because the process of fibreoptic intubation remains quite unpleasant, even with accompanying sedation. In addition, the mandated pre-treatment with glycopyrronium to reduce oral secretions probably also mitigated against reductions in heart rate during DEX treatment. There is some baseline imbalance in systolic blood pressure that complicates the interpretation of this variable in AWAKE.

Some reduction in blood pressure and heart rate is to be expected on instituting effective sedation in a nervous or anxious patient awaiting surgery, so only a part of the change is likely attributable to DEX. Baseline values were taken in the operating room and so consequently may be higher than patients' usual resting values. Changes in the placebo group will also be affected by rescue midazolam.

Despite the large number of cardiovascular AEs reported, only a minority of such patients received any specific treatment (Table 12) indicating that investigators considered most changes not of clinical importance. Hypotension is ordinarily treated either with fluid or small bolus of a vasopressor such as ephedrine, whereas bradycardia responds to anticholinergic therapy such as glycopyrronium or atropine. The use of such treatments is very common in anaesthesia and sedation practice. In clinical practice the practitioner will normally continuously balance the fluid and DEX infusion rates and verbally stimulate the patient to provide optimal sedation and cardiovascular stability, with judicious use of a vasopressor when needed.

Table 25. Treatment related cardiovascular AEs that required treatment during study drug infusion in the MAC study

	DEX 0.5 mcg/kg N=134	DEX 1.0 mcg/kg N=129	Placebo N=63
	No. (%) of subjects		
Cardiovascular events receiving medication			
Bradycardia	0	4 (3.1)	0
Tachycardia	0	0	0
Hypotension	15 (11.2)	9 (7.0)	1 (1.6)
Hypertension	1 (0.7)	1 (0.8)	1 (1.6)

Source: 2005-005 CSR Table 14.3.2.4.1 and Appendices 16.2.7.3 through 16.2.7.5.2.

Bradycardia was much less prominent than hypotension in both MAC and AWAKE studies, with only very few patients receiving anticholinergic treatment (none of the 12 bradycardia events on DEX 0.5 mcg/kg in MAC received treatment). The lower incidence of protocol-defined bradycardia during study drug infusion at 1 mcg/kg loading dose in AWAKE (7.3%) compared to the same dose in MAC (13.2%) may reflect the unpleasant nature of awake intubation.

Hypertension was not identified as a clinical problem in procedural sedation, with a higher incidence on placebo than DEX in both studies. Even so, DEX can cause hypertension in some patients and users should consider this possibility when managing such events, especially if the patient appears adequately sedated.

The incidence of clinically relevant cardiovascular adverse effects should be put in context with other studies and with usual sedative care. Both midazolam and propofol cause hypotension. The systematic reviews conducted by Orion found no difference in the reported incidence of hypotension in studies comparing DEX with midazolam (8.7% vs. 11.4% respectively) or those comparing DEX with propofol (9.3% vs. 8.9% respectively). In a study of DEX (0.5 mcg/kg loading, 0.4 mcg/kg/h maintenance) vs. midazolam (2 mg, single bolus) in 200 patients undergoing inguinal hernia repair (Mishina et al 2017), hypotension and bradycardia occurred in 8 and 14 of 99 DEX-treated patients respectively (2 vs. 8 of 97 midazolam patients respectively) using similar thresholds as the MAC and AWAKE studies. Liao et al (2012) found that hypotension incidence (SBP < 90 mmHg or mean arterial pressure MAP < 60 mmHg) was not different between DEX and midazolam (6.1% vs. 7.1% respectively) in 198 post-thoracotomy patients undergoing transnasal bronchoscopy. In the same study, bradycardia occurred in 13.1% DEX patients vs. 4.0% midazolam patients (p = 0.04, Chi-square) although the threshold for bradycardia was reported as < 60 bpm, which is unusually high. Finally, a Cochrane review (Lewis et al 2015) of alpha-2 agonists in prevention of post-operative shivering found no major cardiovascular complications and that the increased rate of hypotension and bradycardia with DEX were controllable with ephedrine or atropine. Both Liao and Mishini studies reported no increase in the incidence of

hypertension on DEX compared to midazolam, using the same absolute threshold as in the MAC and AWAKE studies (SBP >180 mmHg).

Some episodes of hypotension were recorded in dexmedetomidine subjects during and after leaving PACU. Ephedrine use was recorded in 7 subjects in the DEX 1 mcg/kg group after the end of the infusion, although it is not possible to determine whether this was before or after leaving the PACU. The finding emphasises the need to maintain close monitoring until signs of blood pressure or heart rate effects of dexmedetomidine are fully recovered.

The SmPC for Dexdor already records that patients with pre-existing bradycardia, hypotension, ischaemic heart disease, cerebrovascular disease or severe neurological disorders should be treated with caution because of cardiovascular effects and these warnings seem appropriate also for procedural sedation. In addition, hypotension appeared more likely in elderly patients receiving a loading dose for procedural sedation in the MAC and AWAKE studies. Protocol-defined hypotension increased progressively from 32.6% in patients □65 years to 62.1% in patients >75 years old in the MAC study, although the number of very elderly patients was relatively few. Such an increased risk was not observed in the ICU population and so it is proposed that users should consider using a lower dose of DEX during procedural sedation in elderly patients. The concomitant use of DEX with spinal anaesthesia was not found to increase the risk of hypotension compared to other modes of sedation in 2 meta-analyses (Niu et al 2013, Abdallah et al 2013), although the risk of bradycardia was increased, stressing the need for close monitoring of these patients.

There were no consistent 12-lead ECG changes observed in the phase III studies. Both MAC and AWAKE studies enrolled a significant proportion of patients with extensive systemic morbidity and thus many abnormalities could be seen at both baseline and follow-up, but without indication of DEX-related effects (except on heart rate). The studies did not use central reading or measure conduction intervals.

Overall, the MAH considers that cardiovascular effects of DEX are well defined and readily managed in patients undergoing procedural sedation. The incidence of clinically relevant hypotension appears to be similar to that of midazolam and propofol, although bradycardia is more frequent on DEX. Contrary to earlier data in ICU patients, DEX does not appear to induce clinically significant hypertension at the proposed dose during procedural sedation.

2.5.3. Respiratory effects

Respiratory depression is a common adverse effect of continuous IV sedation with most available drugs in procedural sedation. Inadequate respiration may occur as a consequence both of central respiratory depression and failure to maintain the upper airway. The MAC and AWAKE studies therefore monitored respiratory rate (RR) and SpO2 closely and established thresholds for the reporting of respiratory AEs.

Mean changes in RR and SpO2 were slight in all treatment groups in both studies. RR reduced in the MAC study by -1.0/min, -1.2/min and -1.0/min in the DEX 0.5 mcg/kg, DEX 1 mcg/kg and placebo groups, respectively, during the study drug infusion. The change from baseline was statistically significant in all 3 groups but there was no difference between groups. Small increases in mean SpO2 during both DEX and placebo treatment are presumed to reflect administration of supplemental oxygen (mandatory in AWAKE, optional in MAC) rather than any change in respiratory function.

The use of both relative and absolute thresholds for reporting respiratory AEs led to reporting of respiratory depression AEs in approximately one third of patients in all 3 treatment groups in the MAC study, but a high proportion were due to changes in RR that remained above the clinically relevant

limit of 8/min. Indeed the incidence of clinically relevant respiratory depression using the absolute criteria (either RR < 8/min or SpO2 < 90%) was significantly higher on placebo than in either DEX dose group (Table 13). The difference may be related to the effects of higher doses of midazolam and fentanyl received by placebo patients. As with cardiovascular variables, baseline was established in the operating room when a degree of tachypnoea was likely in many patients (the mean was around 16/min, maximum was 30/min) and so frequent reductions in RR were to be expected with the introduction of effective sedation. For this reason, the number AEs of respiratory depression in the MAC and AWAKE studies may be misleading about the extent of respiratory depression actually observed in those studies, and specifically the effect of DEX on the respiratory system.

Table 26. Incidence of respiratory depression (RD) by different criteria in the MAC study

	DEX 0.5 mcg/kg N=134	DEX 1.0 mcg/kg N=129	Placebo N=63
	No. (%) of subjects		
During study drug infusion			
All RD adverse events	50 (37.3)	44 (34.1)	21 (33.3)
RD events by absolute criteria	5 (3.7)*	3 (2.3)*	8 (12.7)
In PACU			
All RD adverse events	2 (1.5)	2 (1.6)	4 (6.3)
RD events by absolute criteria	0	0	1 (1.6)

Source: 2005-005 CSR Tables 14.2.5.2.1, 14.3.1.4.1 and 14.3.1.4.2

Respiratory depression (RD) is defined as any episode of RR < 8 bpm or SpO_2 < 90%

* p-value <0.05 based on Pearson Chi-square test comparing each DEX arm versus the placebo arm

In the systematic reviews conducted by Orion, the reported relative incidence of hypoxia on DEX was similar in studies comparing DEX with midazolam (5.0% vs. 7.5% respectively) but significantly less in studies comparing DEX with propofol (3.8% vs. 16.5% respectively, p < 0.001). Several published meta-analyses have also addressed this question. Barends et al (2017) found no difference in the incidence of hypoxia in procedural sedation trials between Dex and midazolam. In an analysis of trials comparing DEX with propofol in gastrointestinal endoscopy (Nishizawa et al 2017) there was no significant difference in the risk of developing hypoxia between the treatments, although there were no hypoxia events in 162 DEX-treated patients but 16/164 patients with hypoxia on propofol. In contrast, an analysis of 13 trials in awake fibreoptic nasal intubation (Zhou et al 2016) found significantly fewer hypoxia events on DEX (31/161 patients) compared to alternative sedation (63/164 patients).

Among individual published trials presented in the Summary of Clinical Safety, several reported the incidence of hypoxia or respiratory depression using objective criteria.

There were significantly fewer hypoxia events on DEX vs. remifentanil (5.9% vs. 26.5% respectively, p = 0.021) in the study of awake intubation using a Shikani optical stylet (Xu et al 2016). A very similar incidence of respiratory depression to the MAC study, and using the same thresholds, was seen in patients undergoing inguinal hernia repair (Mishina et al 2017). Respiratory depression was reported in 36/99 DEX patients, significantly less than in midazolam-treated patients (50/97 patients, p=0.03). Using an absolute threshold of SpO2 <90% for >30 seconds as a measure of hypoxaemia, 14.1% of dexmedetomidine patients and 18.2% of midazolam patients developed hypoxaemia during bronchoscopy (Liao at al 2012), which was not significant (although SpO2 was significantly lower on MDZ when measured during bronchoscopy).

Like other sedative agents, deeper sedation with DEX can lead to narrowing of the upper airway. In 50 patients with obstructive sleep apnoea (OSA) undergoing drug-induced sleep endoscopy (Yoon et al 2016), the degree of upper airway narrowing was related to depth of sedation and there was no difference in the pattern of airway obstruction on DEX compared to propofol, although episodes of desaturation were significantly more common on propofol. In contrast, an artificial airway was more often needed on propofol than DEX patients, in a retrospective cohort study in children with OSA (35% vs. 12%, p=0.06, in propofol and DEX patients respectively) (Mahmoud et al 2009).

The concomitant use of midazolam or fentanyl with DEX did not significantly increase the risk of respiratory depression on DEX in the MAC study, although this should be considered when adding other sedative or analgesic drugs with recognised respiratory depressant effects.

Respiratory depression is relatively common during procedural sedation but should normally be readily managed by anaesthetists and others experienced in sedation and airway management. Comparative data on DEX are not consistent but many studies have found a lower degree of respiratory depression on DEX than other sedative regimens.

2.5.4. Recovery from sedation

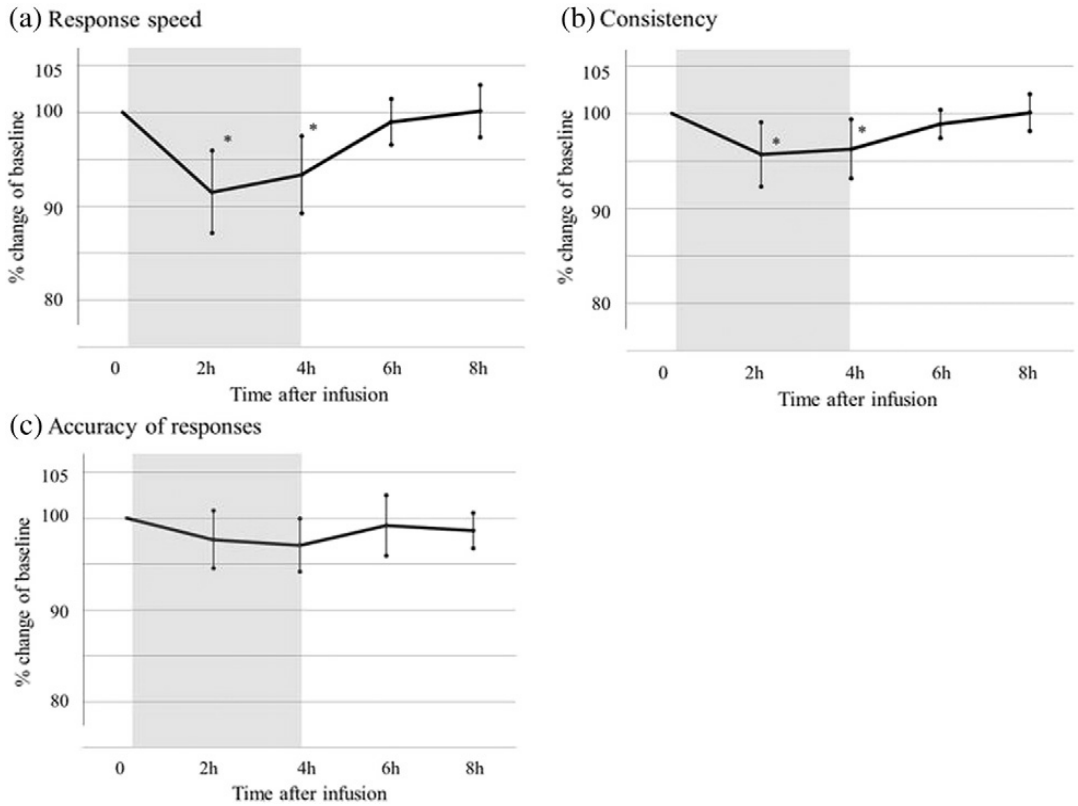
The speed of recovery was examined in the MAC study by assessing the time to achieving an Aldrete score of 9-10. A high Aldrete score (maximum score 10) requires patients to be cooperative with stable cardiovascular and respiratory measures and there was no significant difference between the DEX groups and placebo. In healthy volunteers effects on blood pressure and heart rate persisted for several hours after ending a 4 hour infusion, although measurable cognitive effects recovered more rapidly (Yatabe et al 2016). There was little difference in the speed of recovery following gastrointestinal endoscopy after DEX compared to propofol or midazolam (Demiriran 2007, Wu Y et al 2015). These findings suggest that patients can be expected to have quite normal cognitive function by the time that cardiovascular effects are completely resolved and that recovery practices and expectations for other sedatives should apply also for DEX. Advice for return to normal activities is considered in Section 2.5.5.4.9.

Yatabe et al 2016 looked at the acute cognitive effects of dexmedetomidine in healthy volunteers to measure the time to recovery of cognitive function following administration of DEX in outpatient settings and to provide specific guidance to clinicians. A loading dose of 6 mcg/kg/h (1 mcg/kg) dexmedetomidine was administered over 10 minutes followed by a maintenance infusion of 0.4 mcg/kg/h for a total of 4 hours. Cognitive function was evaluated before the infusion and at 2, 4, 6, and 8 hours after the start of infusion. A brief computerised test battery consisting of 5 tests (CogHealth, Japanese edition) was administered. Response speed, consistency and accuracy of response were measured for the following domains: psychomotor function, attention, visual memory, working memory and visual attention function.

Aggregate scores across all of the 5 domains were obtained. Response speed at 2 hours and 4 hours after infusion started was significantly lower than baseline values (92 ± 8%, $p < 0.0001$; 93 ± 6%, $p < 0.0001$). Consistency was also significantly lower at 2 hours and 4 hours after infusion start (96 ± 7%, $p = 0.0009$; 96 ± 5%, $p = 0.0003$). However, response accuracy during infusion remained unchanged relative to the pre-infusion values (Figure 3).

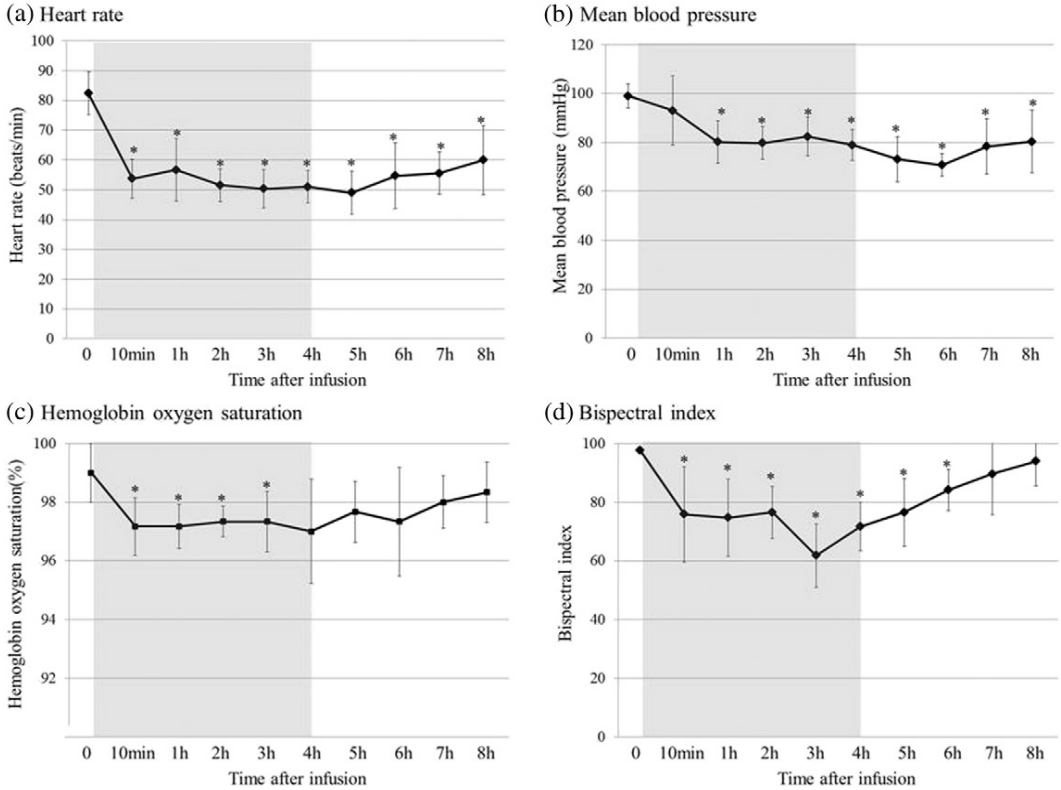
In contrast to haemodynamic parameters most of which were still statistically significantly lower at 8 hours after the start of the infusion (4 hours after infusion end, Figure 4), cognitive function was back to baseline level at 2 hours after the end of infusion.

Figure 3. Cognitive function parameters during and after a 4 hour dexmedetomidine infusion in healthy volunteers



Cognitive function. (a) Response speed; (b) Consistency; (c) Response accuracy. Grey-shaded sections indicate infusion of DEX.* $p < 0.05$ before vs. during infusion of DEX

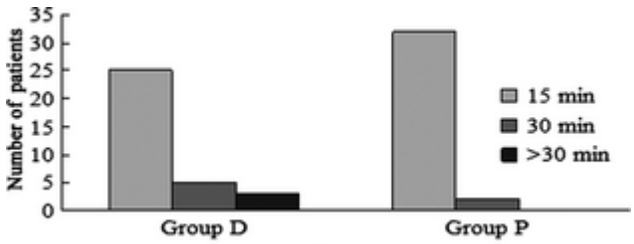
Figure 4. Vital signs during and after a 4 hour dexmedetomidine infusion in healthy volunteers



Vital signs and Bispectral Index. (a) Heart rate; (b) Mean blood pressure; (c) Haemoglobin oxygen saturation; (d) Bispectral index. Grey shaded sections indicate dexmedetomidine infusion.*p < 0.05 before vs. during infusion of DEX

Wu Y et al. 2015 compared propofol vs. DEX in a procedural sedation trial. Discharge was delayed in 3 patients in the dexmedetomidine group (none in the propofol group) - one case of bradycardia, one case of dizziness and nausea and one case of bradycardia and dizziness (p = 0.227).

Figure 5. Number of patients achieving a Modified Post-Anaesthesia Discharge scoring system score of 9-10 after esophagogastroduodenoscopy at 15 min, 30 min and >30 min



Group D = dexmedetomidine group; Group P = propofol group

Demiraran et al 2007 studied patients undergoing upper gastrointestinal endoscopy. The average time to full recovery and the number of patients able to carry out independent transfers was found to be similar between the DEX and MDZ groups. There were also no differences in the number of patients who recovered at the 15, 30 and 45 minute time points between the two groups (Table 27).

Table 27. Time to recovery data in patients after upper gastrointestinal endoscopy

Variable	MDZ (N = 25)	DEX (N = 25)	p-value
Independent transfer, n	17	13	0.11
Time to full recovery, min[a]	37.6 ± 11	42 ± 12.5	0.30
Patients fully recovered, n (%)			
15 min	12 (48)	10 (40)	0.56
30 min	20 (80)	18 (72)	0.74
45 min	25 (100)	25 (100)	0.99

[a] Mean ± SD

Fan et al 2013 in a study of 60 patients found all patients treated with DEX and MDZ were ready for discharge at 30 mins after completion of dental surgery.

2.5.5. Laboratory findings

The effects of DEX on routine biochemistry and haematology laboratory tests were investigated in earlier studies, based on much more prolonged exposure in a critically ill population. In the procedural sedation phase III studies the exposure was necessarily short and so no new safety findings were to be expected compared to the review in the 2010 MAA. The only notable finding in the safety laboratory tests was a significant increase in serum glucose compared to baseline, that appeared to be larger in patients with a history of diabetes (Orion post-hoc analysis). Alpha-2 agonists are known to reduce insulin secretion, which is probably at least partly related to alpha-2 mediated inhibition of beta cells (Angel et al 1988). Given the assumed mechanism for this effect, the serum glucose increases are likely to be short-lived after the DEX infusion is stopped and to be of no clinical significance.

2.5.6. Safety in special populations

The impact of sub-populations on the safety of DEX was evaluated in depth in the 2010 MAA and no specific guidance was developed for different sub-populations of patients based on demographic factors. There is no reason to consider that any subgroups would be inherently at greater risk from DEX treatment during procedural sedation, or that there would be important new sub-groups not addressed in the earlier approval. However the use of a loading dose represents an important change, necessitating some reanalysis of subgroups.

Elderly

AEs in the pooled database of phase III studies are displayed in Table 28 according to different age groups. In the DEX group it appeared that the frequency of protocol-defined hypotension increased with age occurring in 47.0% vs. 71.2% vs. 72.4% of patients in ≤65 years, >65-75 years and >75 years groups, respectively. This increase was not reflected in the placebo group.

No other events on DEX appeared to follow an age-related pattern of incidence. In the placebo group the proportions of patients with tachycardia (19.3%) in the ≤65 years group was higher than in the >65-75 years (9.1%) and >75 years (12.5%) groups, although there were few patients in the older age groups.

The frequency of protocol-defined hypotension appeared to increase with age on DEX treatment, occurring in 47.0% vs. 71.2% vs. 72.4% patients in up to 65 years, 65-75 years and > 75 years groups

respectively in the pooled phase III data, without a similar change in the placebo group. The number of hypotension events also appeared higher in the elderly during the first 15 minutes after starting the infusion, suggesting some of the increased risk was related to the loading dose. The finding should be interpreted with a degree of care since the number of patients in the older age groups becomes more limited, making the confidence in the size of the difference weak. Also, this predominantly reflects changes from baseline rather than the occurrence of hypotension in need of treatment and the number of patients receiving treatment for hypotension in these studies was too low to support more detailed analysis. Still, it is wise to consider whether a lower dose would be appropriate when treating an elderly patient.

There were no indications of age-related effects for other AEs and neither race nor gender appeared to affect the safety of DEX in procedural sedation. An analysis of the MAC study did not show any greater risk for AEs in patients receiving anti-hypertensive drugs, predominantly beta-blocks and renin-angiotensin system blockers.

Spinal or epidural anaesthesia

The MAC and AWAKE studies excluded patients having spinal or epidural anaesthesia but this represents a relevant clinical situation where DEX can be expected to be used in clinical practice. There are many published studies combining DEX with spinal anaesthesia and most patients tolerate the treatment well. Although both DEX and spinal anaesthesia cause hypotension and bradycardia, the risk of hypotension was not found to be increased in a meta-analysis (Niu et al 2013), although there was an increased risk of bradycardia. The risk may be further increased in the elderly (Hong et al 2012). The combination of DEX with spinal anaesthesia appears safe provided patients are closely monitored and well hydrated.

Obstetric use

A number of studies have administered DEX to patients during caesarean section. As with all sedative agents, such administration will lead to foetal exposure to dexmedetomidine, although so far no adverse effects on the foetus have been observed. In the DEX-09-08 and DEX-11-06 studies dexmedetomidine was administered to newborn infants (as early as 28 weeks gestation) without specific safety concerns. The use of DEX at the time of caesarean section is likely to be in combination with general or spinal anaesthesia and so caution is needed in case of additive adverse effects. Experience of the use of DEX during earlier pregnancy is very limited and no specific guidance can be given. Overall the administration of DEX during pregnancy is not recommended and should only be undertaken if the benefit to the patient is considered to outweigh the potential (partly unknown) risks.

Apart from MAC and AWAKE, data are presented in a wide range of different patient groups and procedures, suggesting that there are no specific uses for which the safety of DEX would constitute particularly high risk, provided it is administered under appropriate conditions of monitoring by appropriately qualified professionals.

Table 28. AEs during study treatment and follow-up by age category in the pooled phase III studies (events reported in > 2 patients)

Preferred Term	All DEX (N=318)			PBO (N=113	
	≤ 65 years (n = 230)	> 65-75 years (n = 59)	> 75 years (n = 29)	≤ 65 years (n = 83)	> 65-75 yea (n = 22)
	Patients n (%) Events n			Patients n (%) Ev	
Hypotension	108 (47.0) 122	42 (71.2) 46	21 (72.4) 22	24 (28.9) 28	7 (31.8) 7
Respiratory depression	76 (33.0) 83	18 (30.5) 18	10 (34.5) 11	23 (27.7) 23	4 (18.2) 5
Hypertension	31 (13.5) 35	7 (11.9) 7	3 (10.3) 3	18 (21.7) 24	7 (31.8) 7
Bradycardia	32 (13.9) 35	10 (16.9) 10	2 (6.9) 2	2 (2.4) 2	1 (4.5) 1
Tachycardia	12 (5.2) 12	5 (8.5) 5	-	16 (19.3) 20	2 (9.1) 2
Bradypnoea	12 (5.2) 12	4 (6.8) 4	-	4 (4.8) 4	2 (9.1) 2
Dry mouth	6 (2.6) 6	2 (3.4) 2	-	1 (1.2) 1	-
Hypoxia	5 (2.2) 5	2 (3.4) 2	-	2 (2.4) 2	-
Respiratory rate decreased	2 (0.9) 2	1 (1.7) 1	-	4 (4.8) 4	-
Nausea	9 (3.9) 9	-	1 (3.4) 1	2 (2.4) 2	-
Headache	6 (2.6) 6	-	-	2 (2.4) 2	-
Dizziness	2 (0.9) 2	-	-	1 (1.2) 1	-
Anxiety	2 (0.9) 2	-	-	-	1 (4.5) 1
Procedural hypotension	1 (0.4) 1	1 (1.7) 1	1 (3.4) 1	-	-
Procedural nausea	2 (0.9) 2	-	-	1 (1.2) 1	-
Procedural pain	1 (0.4) 1	1 (1.7) 1	-	1 (1.2) 1	-
Oropharyngeal pain	1 (0.4) 1	-	-	2 (2.4) 2	-
Pruritus	2 (0.9) 2	-	-	2 (2.4) 2	-
Diastolic hypertension	1 (0.4) 1	1 (1.7) 1	-	1 (1.2) 1	-

2.5.7. Safety related to drug-drug interactions and other interactions

There are no drug interaction studies performed specific to this application and neither are there significant new interaction risks related to procedural sedation. In the 2010 MAA it was concluded that the interaction risk for DEX is low and most drugs commonly used in patients undergoing surgical and diagnostic procedures are also common in an ICU environment.

Addition of midazolam or fentanyl to DEX treatment in the MAC study identified only a modest increase in AEs, mostly respiratory depression, which was to be expected given the known adverse effects of those drugs. A similar effect could have been expected in the placebo group but very few placebo patients did not receive midazolam.

The analysis of patients with and without pre-operative antihypertensive drug use did not suggest any clinically relevant increased risk for cardiovascular instability. There was no increase in the risk of bradycardia despite many such patients receiving beta-blockers.

Table 29. Summary of AEs in ≥ 2% of patients in any treatment group during study drug infusion: with and without preoperative antihypertensive drug use

Adverse Event	DEX 0.5 mcg/kg N = 134		DEX 1 mcg/kg N = 129		PBO N = 63	
	DEX only n = 68	DEX + Anti-H[a] n = 66	DEX only n = 61	DEX + Anti-H[a] n = 48	PBO only n = 34	PBO + Anti-H[a] n = 29
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Adverse Event	DEX 0.5 mcg/kg N = 134		DEX 1 mcg/kg N = 129		PBO N = 63	
	DEX only n = 68	DEX + Anti-H[a] n = 66	DEX only n = 61	DEX + Anti-H[a] n = 48	PBO only n = 34	PBO + Anti-H[a] n = 29
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hypotension	32 (47.1)	32 (48.5)	24 (29.6)	17 (35.4)	8 (23.5)	9 (31.0)
Respiratory depression	25 (36.8)	25 (37.9)	26 (32.1)	18 (37.5)	13 (38.2)	8 (27.6)
Bradycardia	6 (8.8)	6 (9.1)	14 (17.3)	3 (6.3)	2 (5.9)	1 (3.4)
Hypertension	3 (4.4)	8 (12.1)	6 (7.4)	5 (10.4)	3 (8.8)	5 (17.2)
Tachycardia	2 (2.9)	2 (3.0)	5 (6.2)	2 (4.2)	2 (5.9)	5 (17.2)
Dry mouth	0	4 (6.1)	3 (3.7)	1 (2.1)	0	0
Hypoxia	1 (1.5)	1 (1.5)	0	1 (2.1)	0	2 (6.9)
Headache	2 (2.9)	0	1 (1.2)	0	0	0
Agitation	0	0	0	1 (2.1)	0	0
Dysphoria	0	0	0	1 (2.1)	0	0
Restlessness	0	0	0	1 (2.1)	0	0
Tremor	0	0	0	0	1 (2.9)	0

Anti-H = antihypertensive medications

[a] Patients who were taking antihypertensive medications (beta-blockers, calcium-channel blockers, diuretics, ACE-inhibitors and alpha/beta blockers) prior to surgery.

2.5.8. Overdose, abuse and medication errors

There is little additional data from post-marketing surveillance on overdose, abuse or medication errors since the 2011 approval of Dexdor in the EU. DEX does not appear to be associated with intentional abuse or intentional overdose. In those cases of accidental overdose, involving multiples of the intended dose (including giving the drug undiluted), patients have suffered predominantly bradycardia, hypertension, respiratory depression and deep sedation as anticipated.

As in the ICU, procedural sedation ordinarily takes place in a closely regulated hospital environment, so significant medication errors can be expected to be uncommon. The use of a loading dose slightly increases the risk for error, simply because of the increased complexity, but still should not be a challenge for personnel experienced in providing sedation. Errors of dilution or of calculating the infusion rate are equally relevant to any drug given by continuous IV infusion. A further potential source of medication error is of failing to turn the infusion rate down at the end of the loading dose: close monitoring of the patient (see Section 2.5.5.4.9) should identify such a mistake rapidly.

2.5.9. Dose considerations

The dosing scheme of dexmedetomidine in procedural sedation is necessarily different to that for ICU sedation. In the ICU, most patients who receive DEX have already been receiving another sedative drug or general anaesthesia and therefore there is not generally a need for a rapid onset of action. In this setting a loading dose is not normally needed and thus the benefits of the rapid onset do not justify the associated AEs. In procedural sedation a rapid onset of effect is generally needed and so a loading/bolus dose is standard practice with established sedative agents. The loading dose is well established for DEX in this indication and for some short procedures a subsequent maintenance infusion has not been required.

A loading dose has been used in almost all published studies of IV DEX in procedural sedation and in all those studies discussed in this application. While 1 mcg/kg over 10 minutes is the most typical loading dose, many studies have used 0.5 mcg/kg or even less, and some have given the infusion

faster (over 5 minutes) or slower (over up to 20 minutes). The maintenance DEX dose has also been somewhat variable, often starting at around 0.6-0.7 mcg/kg/h, but frequently lower, especially where the sedative need is considered lighter. While the maximum DEX continuous dose for ICU use in the EU is 1.4 mcg/kg/h, in the USA (and in many other territories at the time of the published studies) it remains at 0.7 mcg/kg/h and this is likely to have been an important determinant for the dose selection in many existing procedural sedation studies.

The use of a loading dose of DEX in procedural sedation studies is supported by the available data. Aside from the clinical need for a more rapid action, the loading dose is not the main driver of the cardiovascular effects of DEX. In the combined MAC and AWAKE studies only 9.2% patients had protocol-defined hypotension within the first 15 minutes (during and after the loading dose infusion) in patients receiving DEX 1 mcg/kg loading dose. The incidence of hypertension during this same period was very similar (8.7%) and not different to the incidence on placebo. Important changes in heart rate were uncommon during this time, protocol-defined bradycardia occurring in only 2.7% patients.

The typical dose of 1mcg/kg loading followed by around 0.7 mcg/kg/h (with range between 0.2 to 1.0 mcg/kg/h), as used in the MAC and AWAKE studies, appears to be a good standard approach. The dose was effective and only 7% of patients had treatment-related hypotension that required a vasopressor during the DEX infusion (although some patients will continue to need a vasopressor during PACU). Bradycardia sufficient to require treatment was uncommon (3.1% DEX 1 mcg/kg patients) and responded rapidly to anticholinergic treatment. Health care professionals experienced in anaesthesia and sedation are very familiar with the identification and treatment of such events since hypotension at least is a common adverse effect of other sedatives.

This proposed dose schedule appears suitable for most patients. The combination of the MAC and AWAKE studies includes patients who will have both quite challenging and unpleasant procedures and those for whom stimulation is limited. Still, there are situations where alternative dose schedules may be considered.

The smaller loading dose (0.5 mcg/kg) did not actually provide an improved safety profile in the MAC study. This may be partly because the majority of adverse effects are related to the maintenance infusion rather than the loading dose, but might also reflect that peripheral vasoconstriction at higher concentrations of DEX will tend to counteract hypotension, despite deeper sedation. Nevertheless it may be prudent to select a lower dose when treating patients considered at higher risk, for example older, frail patients. 0.5 mcg/kg is the only smaller loading dose for which adequate data are available so, although some clinicians have reported using even lower doses, there is insufficient data to recommend this. Some limited experience exists on the infusion of the loading dose over a longer period to reduce the risk of AEs. In study 3005010, presented in the 2010 MAA, patients admitted to ICU after coronary artery bypass received the 1 mcg/kg loading dose over either the usual 10 or 20 minutes. There was some reduction in the speed of blood pressure change with the slower infusion but no change in the reporting of cardiovascular AEs. Such an approach can be considered in individual patients but may not generally be of value and might exceed the time available for establishing sedation in many clinical situations.

There is no available data on the use of maintenance DEX infusions >1 mcg/kg/h or loading dose > 1 mcg/kg over 10 minutes in procedural sedation and such doses cannot be recommended.

2.5.10. Safety monitoring

The MAC and AWAKE studies were both performed in a hospital operating room environment with an anaesthetist continuously present. There are many different clinical environments where procedural sedation might be performed and some minimum standards are needed to ensure that patient safety is maintained. These relate to the facilities, the operator and the level of patient monitoring and are not specific to dexmedetomidine.

The requirements for clinical facilities have been described in a number of publications (e.g. Calderwood et al 2014) and include equipment for maintaining patient airway and ventilation, oxygen supply, suction and other resuscitative equipment.

The adverse effects of dexmedetomidine, and other intravenous sedatives, are readily managed by experienced professionals. Dexmedetomidine sedation should be administered only by a professional trained in airway and continuous IV sedation management and in the identification and treatment of events such as hypotension, bradycardia and respiratory depression. That person should be dedicated to the sedation management and not involved in other tasks such as assisting with or performing the procedure itself.

The appropriate level of monitoring is determined by the condition of the patient and the nature of the procedure, and the following is intended as a minimum standard. Users should monitor the level of sedation regularly. This particularly involves maintaining verbal contact with the patient when possible. Continuous cardiac monitoring is the most effective method to identify bradycardia and should be used in all patients treated with dexmedetomidine. Regular measurements of blood pressure, ideally using an automated sphygmomanometer, should also be performed in order to identify hypotension or hypertension that may need treatment. The use of respiratory monitoring is not consistent. SpO2 should be monitored in all patients but hypoxaemia is not a reliable monitor for respiratory depression, especially when supplemental oxygen is provided (a routine practice for many users). Regular verbal contact contributes to respiratory monitoring but capnography may be appropriate for situations where the sedation operator is not able to directly see patient ventilation (for example because of equipment such as magnetic resonance imaging). Close respiratory monitoring would also be appropriate during deep sedation: although this should not normally be a target for dexmedetomidine it may be relevant if high doses of other sedatives or opioid analgesics are given concomitantly. Close observation of the patient should continue for at least an hour after the dexmedetomidine infusion is discontinued, as a number of episodes of hypotension were reported during this time in the MAC study.

The level of continuous monitoring during sedation for procedures is the subject of multiple guidelines or published standards but without complete consensus. See the review by Sheahan et al (2014) for further discussion.

Some patients receiving dexmedetomidine for procedural sedation will be discharged home on the same day and the same precautions that are applied to other IV sedation agents should be applied to dexmedetomidine use. Patients should remain under medical supervision for at least a further hour after completing close monitoring, or longer if the effects of dexmedetomidine are persistent and it is good practice to ensure that patents are discharged with a suitable responsible third person after receiving sedation. It is difficult to give firm rules for a return to normal activities, including driving or other hazardous tasks and the operator should provide personalised information according to the patient's condition, comorbidities and circumstances according to usual practice. Such advice should also extend to other drugs with sedative effects and alcohol. The cognitive effects of DEX had a shorter duration than cardiovascular effects in healthy volunteers but still the period of caution should extend longer than the measureable effects of dexmedetomidine.

Adverse event data from the literature

Xu et al (2016) compared the efficacy and safety of dexmedetomidine versus remifentanil for sedation during awake intubation[8] in a RCT in 68 patients aged 18-70 years, ASA I–III. The DEX group received a loading dose of 1.0 mcg/kg dexmedetomidine over 10 min followed by a continuous infusion of 0.7 mcg/kg while the remifentanil (REMI) group received a target-controlled infusion of remifentanil (initial target 2.5 ng/ml, increased to 3ng/ml after 10 minutes).

Table 30. Haemodynamic changes during awake intubation

Index	Group	T1	T2	T3	T4	p (between groups)
SBP (mmHg)	DEX	130 ± 18	120 ± 18	127 ± 30	148 ± 16	0.630
	REMI	131 ± 14	122 ± 14	125 ± 15	137 ± 13	
DBP (mmHg)	DEX	77 ± 13	72 ± 11	75 ± 11	87 ± 12	0.761
	REMI	79 ± 10	73 ± 13	74 ± 12	82 ± 13	
HR (min^{-1})	DEX	79 ± 16	72 ± 16	78 ± 15	86 ± 14	0.682
	REMI	76 ± 12	72 ± 12	77 ± 11	85 ± 12	

N = 34 each group
Data are presented as mean ± standard deviation. T1, baseline; T2, 10 min after study drug infusion; T3, pre-intubation; T4, 1 min after intubation

Table 31. AEs during airway management

Adverse event	DEX N = 34	REMI N = 34	p-value
Hypotension	3 (8.8)	1 (2.9)	0.303
Hypertension	3 (8.8)	6 (17.6)	0.283
Tachycardia	7 (20.6)	9 (26.5)	0.567
Bradycardia	2 (5.9)	0 (0)	0.151
Hypoxia	2 (5.9)	9 (26.5)	0.021
Loosening of teeth	0 (0)	0 (0)	1.000
Injury to lip or oral mucosa	0 (0)	0 (0)	1.000
Postoperative sore throat	16 (47.1)	18 (52.9)	0.628
Hoarseness	2 (5.9)	2 (5.9)	1.000

Data are given as number (proportion, %). Baseline values of SBP, DBP and SpO_2 were used to define AEs. Hypotension was defined as SBP < 80 mmHg, DBP < 50 mmHg or SBP decreased ≤ 30% below baseline values. Hypertension was defined as SBP > 180 mmHg, DBP > 100 mmHg or an SBP increased ≥ 30% higher than baseline values. Bradycardia was defined as HR < 45 min−1 or a decrease to ≤ 30% below baseline. Tachycardia was defined as HR 120 min−1 or an increased 30% higher than baseline values. Hypoxia was defined as SpO_2 ≤ 90% or a decrease by 10% of the baseline saturation

Lewis et al (2015) published a Cochrane Database systematic review on alpha-2 adrenergic agonists for the prevention of shivering following general anaesthesia[9]. Four studies systematically evaluated bradycardia and hypotension and these are summarised in Table 32. In all cases DEX was given in conjunction with general anaesthesia. No major cardiovascular complications were reported. There was no mortality reported.

More bradycardia and hypotension occurred in the DEX group, either at a single dose of 1.0 mcg/kg or a loading dose of 1.0 mcg/kg followed by a maintenance infusion. Hypotension and bradycardia were controllable with ephedrine and atropine and no clinically important haemodynamic derangements occurred.

Table 32. Studies evaluating hypotension and bradycardia after dexmedetomidine administration for the prevention of post-operative shivering

<table>
<tr><th>Reference</th><th>Investigational drugs</th><th>Bradycardia</th><th>Hypotension</th></tr>
<tr><td>Bajwa 2012</td><td>DEX 1 mcg/kg IV over 10 minutes, 30 minutes before end of surgery
Control group saline</td><td colspan="2">Postoperative mean results
<table>
<tr><th></th><th>DEX (N = 40)</th><th>Saline (N = 40)</th><th>p-value</th></tr>
<tr><td>HR/min</td><td>65.28 ± 4.92</td><td>78.56 ± 6.64</td><td>0.008</td></tr>
<tr><td>MAP mmHg</td><td>77.28 ± 5.64</td><td>87.52 ± 8.18</td><td>0.012</td></tr>
</table>
The occurrence of bradycardia or hypotension was not reported</td></tr>
<tr><td>Elvan 2008</td><td>DEX 1 mcg/kg IV over 10 minutes followed by an infusion at 0.4 mg/kg/h
Control group saline</td><td>Bradycardia (< 45/min and received atropine)
DEX 19/40 patients
Saline 8/40 patients (p< 0.05).</td><td>Hypotension (received ephedrine)
DEX 3/40 patients
Saline 2/40 patients.</td></tr>
<tr><td>Karaman 2014</td><td>DEX 1 mcg/kg IV over 10 minutes followed by infusion of 0.5 mcg/kg/h
Control group saline</td><td>“Mean HRs were lower in the dexmedetomidine group after onset of the infusion at all measuring times except for 15 min. Significantly more patients in the dexmedetomidine group needed atropine to treat intraoperative bradycardia than in the placebo group (p > 0.05)”. Data not shown.
Bradycardia (received atropine):
DEX 11/30 patients
Saline 5/30 patients</td><td>“MAPs were lower in the dexmedetomidine group, especially after induction of anaesthesia, at 60 min, and before extubation.” Data not shown.
Hypotension (received ephedrine)
DEX 2/30 patients
Saline 0/30 patients</td></tr>
<tr><td>Kim 2013</td><td>DEX 0.5, 0.75 or 1.0 mcg/kg IV over 10 minutes, 30 minutes before end of surgery
Control group saline</td><td>Intraoperative bradycardia (< 50/min received atropine)
DEX 0.5 mcg/kg 3/30 patients
DEX 0.75 mcg/kg 6/30 patients
DEX 1 mcg/kg 5/30 patients
Saline 0/30 patients</td><td>Intraoperative hypotension (SBP < 80 mmHg received ephedrine)
DEX 0.5 mcg/kg 1/30 patients
DEX 0.75 mcg/kg 2/30 patients
DEX 1 mcg/kg 2/30 patients
Saline 0/30 patients</td></tr>
</table>

The systematic reviews comparing the clinical efficacy of dexmedetomidine with midazolam or propofol in procedural sedation also recorded the reported frequency of hypotension and hypoxia (as an indicator of respiratory depression). Note that the studies included may have used a variety of definitions or other criteria to assess the presence of hypotension and hypoxia.

Table 33. Incidence of hypotension and hypoxia in a systematic review of dexmedetomidine vs. midazolam in procedural sedation

Reference	Procedure	DEX dose		DEX			Midazolam		
		Loading mcg/kg	Maintenance[b] mcg/kg/h	N	Hypotension n (%)	Hypoxia n (%)	N	Hypotension n (%)	Hypoxia n (%)
Frolich 2011	Healthy volunteers	TCI		20	-	0	20	-	0
Alhashemi 2006	Cataract surgery	1	0.1-0.7	22	0	0	22	0	0
Apan 2009	Cataract surgery	-	0.25	30	0	0	30	0	0
Mishina 2017	Inguinal hernia repair	0.5	4	99	8	-	97	2	-
Peng 2016	Lumbar disc surgery	0.5	0.5	30	0	0	30	0	2
Kaya 2010	Bupivacaine spinal anaesthesia	0.5		25	2	0	25	0	0
Liao 2012	Flexible bronchoscopy	1	0.5	99	6	14	99	7	18
Cheung 2007	Third molar surgery	1	-	30	-	6	30	-	4
Demiraran 2007	Upper endoscopy	1	0.2	25	0	0	25	0	2
Fan 2013	Dental surgery	1[a]	0.2	30	0	0	30	0	0
Frolich 2013	Effect of sedation on pain perception	TCI		28	-	-	27	-	-
Ustun 2006	Outpatient third molar surgery	1		20	-	-	20	-	-
Jo 2016	Spinal anaesthesia	1	0.5	58	18	0	58	38	0
Takimoto 2011	Endoscopic submucosal dissection of gastric cancer	0.25	0.4	30	5	0	30	4	4
Total									
Hypotension				448	39 (8.7)		446	51 (11.4)	
Hypoxia				399		20 (5.0)	399		30 (7.5)

- = data not reported; TCI = Target Controlled Infusion

[a] Actually 6 mcg/kg/h until adequate sedation, 1 mcg/kg is estimated

[b] Often starting dose without upper limit stated

Table 34. Incidence of hypotension and hypoxia in a systematic review of dexmedetomidine vs. propofol in procedural sedation

Reference	Procedure	DEX dose		DEX			Propofol		
		Loading mcg/kg	Maintenance mcg/kg/h	N	Hypotension n (%)	Hypoxia n (%)	N	Hypotension n (%)	Hypoxia n (%)
Frolich 2011	Healthy volunteers	TCI		20	-	0	20	-	0
Frolich 2013	Effect of sedation on pain perception	TCI		28	-	-	31	-	-
Salem 2016	Shockwave lithotripsy	1	0.3	26	0	-	26	0	-
Sethi 2015	Dilatation and curettage	1	0.5	25	2	0	25	13	13
Cho 2015	Sleep endoscopy	1	0.2-1.4	20	0	9	22	1	17
Eberl 2016	Endoscopic oesophageal procedures	1	0.7-1.0	32	-	-	31	-	-
Kasuya 2009	Healthy volunteers	TCI		9	-	-	9	-	-
Sriganesh 2015	Diagnostic cerebral angiography	1	0.5	30	2	0	30	0	1
Kaygusuz 2008[b]	Shockwave lithotripsy	1	0.2	20	0	1	20	0	3
Loh 2016	Magnetic resonance imaging	1	0.2-0.7	15	2	0	15	0	0
Nallam 2017	Middle ear surgeries	1	0.4	50	16	0	50	7	0
Kim 2017	Monitored anaesthesia care	1	0.4	29	0	4	28	0	12
Wang 2017	Inguinal hernia repair	0.5		40	-	0	40	-	0
Tsai 2010	Fibreoptic nasotracheal intubation	1		20	1	0	20	0	1
Kim 2015[a]	Endoscopic submucosal dissection	0.5	0.3-0.7	29	0	0	30	0	0
Wu Y 2015	Oesophago-gastro-duodenoscopy	1	0.5	33	-	-	34	-	-
Takimoto 2011	Endoscopic submucosal dissection of gastric cancer	0.25	0.4	30	5	0	30	0	8
Wang 2014	Laser in situ keratomileusis	0.3	0.5	10	-	0	10	-	0
Ma 2012	Coblation-assisted upper airway procedure	1	0.7	30	2	0	30	8	6
Total									
Hypotension				324	30 (9.3)		326	29 (8.9)	
Hypoxia				368		14 (3.8)	370		61 (16.5)

- = data not reported; TCI = Target Controlled Infusion

[a] Data from DEX-remifentanil and propofol-remifentanil combinations presented

[b] 'Hypoxia' in this study was the number of patients receiving oxygen supplementation because of $SpO_2 \leq 92\%$

There was a high level of variability in the reporting of hypotension and hypoxia between studies for both the midazolam and propofol systematic reviews. The incidence of reported hypotension was similar for dexmedetomidine, midazolam and propofol (ranging between 8.7 to 11.4%). Hypoxia was reported in 3.8% and 5.0% of dexmedetomidine patients, 7.3% midazolam patients and 16.5% propofol patients.

Respiratory events

The majority of patients having AE respiratory depression in the MAC study were the result of meeting the protocol-defined threshold for relative change from baseline (<25% reduction) in respiratory rate. In the table below it can be seen that the number of patients meeting the absolute criteria for either respiratory rate or S_pO_2 was very much lower, and significantly less for both DEX groups than placebo. During the study drug infusion such cases of absolute respiratory depression occurred in 3.7% vs. 2.3% vs. 12.7% of DEX 0.5 mcg/kg, DEX 1 mcg/kg and placebo groups respectively.

Table 35. Number (%) of patients having at least one incidence of respiratory depression by study time point using absolute threshold criteria (MAC study)

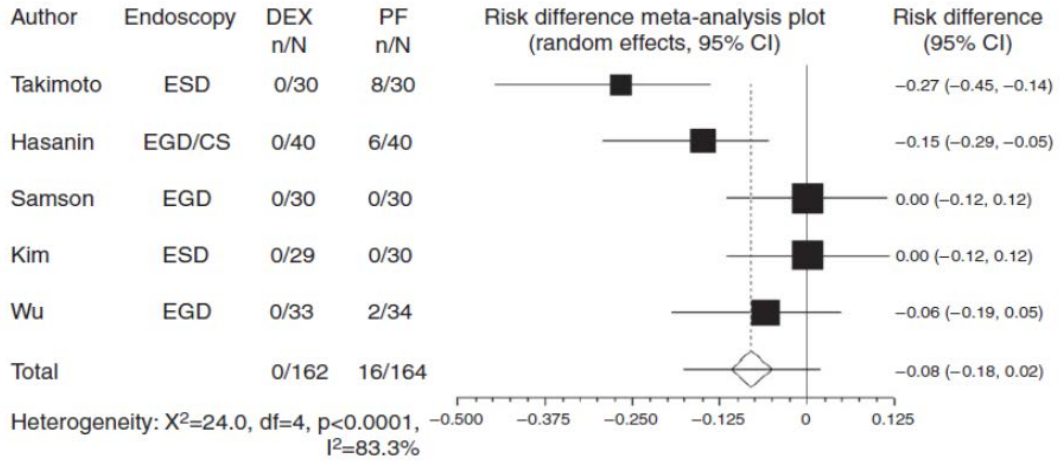
Timepoint	DEX 0.5 mcg/kg N = 134		DEX 1 mcg/kg N = 129		PBO N = 63
	n (%)	p-value*	n (%)	p-value*	n (%)
Infusion	5 (3.7)	0.018	3 (2.3)	0.004	8 (12.7)
PACU	0	0.144	0	0.151	1 (1.6)
Overall	5 (3.7)	0.018	3 (2.3)	0.004	8 (12.7)

Respiratory depression is defined as any episode of RR < 8 bpm or SpO_2 < 90%
* p-value based on Pearson Chi-square test comparing each DEX arm versus the placebo arm

Barends et al 2017 in systematic review and meta-analysis of 11 (dexmedetomidine vs. midazolam) procedural sedation trials detected no difference in the incidence of respiratory events between the two groups. 20 hypoxia events were reported in 281 dexmedetomidine-treated patients, compared to 24 events among 280 midazolam-treated patients (p = 0.52).

Nishizawa et al 2017 in a meta-analysis of gastrointestinal endoscopy trials also did not identify any significant difference in the incidence of hypoxia between dexmedetomidine and propofol treated groups: –0.080 (95% CI: –0.178 to 0.018; p = 0.11) (Figure 6). Hypoxia was reported in 5 out of the 6 studies included in this meta-analysis.

Figure 6. Forest plot displaying the risk difference and 95% CI of each study for hypoxia, dexmedetomidine vs. propofol in gastrointestinal endoscopy

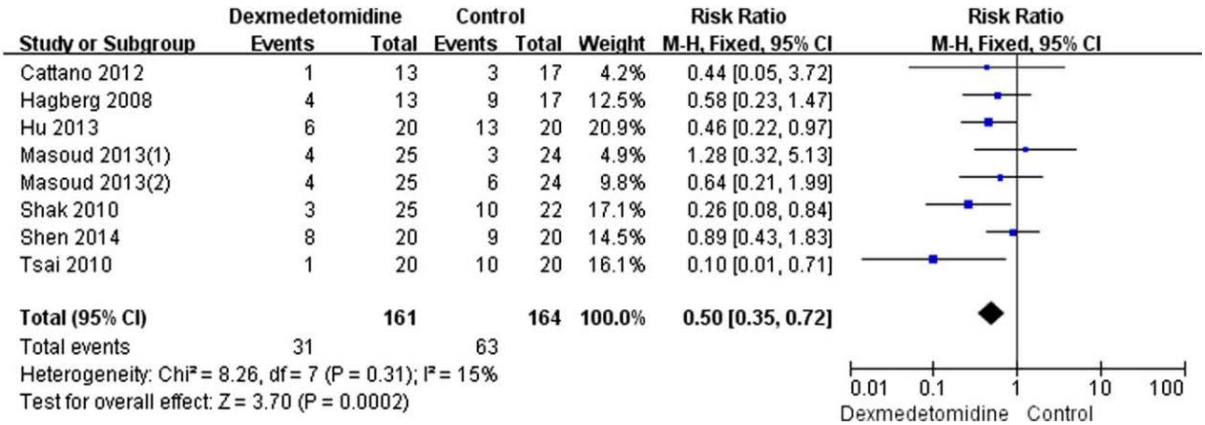


DEX: dexmedetomidine; PF: propofol; EGD: upper gastrointestinal endoscopy; ESD: endoscopic submucosal dissection; CS: colonoscopy

Hwang et al 2017 in a meta-analysis evaluating nasal surgery trials detected no difference in the incidence of intraoperative desaturation (relative risk 1, 95% CI 0.10-9.78) between DEX and control (propofol or midazolam or general anaesthesia) groups.

Zhou et al 2016 in a meta-analysis of 13 trials of awake fiberoptic nasal intubation found that DEX was associated with a lower incidence of hypoxia during awake intubation (relative risk 0.32, 95% CI 0.15–0.70) (Figure 7). The control drugs used in the trials included remifentanil, propofol, midazolam, sufentanil and fentanyl.

Figure 7. Meta-analysis of hypoxia events during awake fibreoptic intubation



Mishina et al (2017)[10] conducted a single-blind RCT in 200 patients undergoing inguinal hernia repair with local anaesthesia, assigning patients to either DEX (0.5 mcg/kg loading dose then 0.4 mcg/kg/h maintenance infusion) or midazolam (2 mg, single bolus) sedation. The AEs reported are shown in Table 36. The criteria for respiratory depression were very similar to those in the MAC and AWAKE studies and showed a similar incidence of respiratory depression; however this occurred significantly more frequently on midazolam. Hypotension and bradycardia were more common on dexmedetomidine than midazolam.

Table 36. Adverse events reported in patients undergoing inguinal hernia repair under dexmedetomidine or midazolam sedation

Adverse event	Dexmedetomidine (n = 99)	Midazolam (n = 97)	p-value[a]
Respiratory depression	36	50	0.03
Hypertension	1	2	NS (0.49)
Hypotension	8	2	NS (0.054)
Bradycardia	14	8	NS (0.19)
Delirium	1	2	NS (0.49)

[a] by Chi-square. NS = nonsignificant
Respiratory depression: RR < 8 bpm, 25% decrease, SpO2 < 90% or 10% reduction or O_2 administration required
Hypotension: SBP < 80 mmHg, 30% decrease or DBP < 50 mmHg
Bradycardia: HR < 40 bpm or 30% decrease
Hypertension: SBP > 180 mmHg, 30% increase or DBP> 110 mmHg

Liao et al (2012) randomised 198 patients undergoing transnasal flexible bronchoscopy in the ICU after thoracic surgery to DEX (up to 1 mcg/kg loading over 10 minutes, then maintenance infusion starting at 0.5 mcg/kg/h) or MDZ (2 mg bolus with further 1 mg as required) along with supplemental oxygen by nasal cannula. The mean S_pO_2 was significantly lower at 5 minutes after the start and at the end of the bronchoscopy procedure in midazolam-treated patients. SBP and HR were significantly lower on dexmedetomidine at the same time-points. The AEs recorded, along with definitions applied, are presented in Table 37.

Table 37. Adverse events occurring during flexible bronchoscopy following thoracic surgery

Adverse events	Dexmedetomidine (n = 99) n (%)	Midazolam (n = 99) n (%)	Statistical significance
Hypertension	4 (4.0)	12 (12.1)	NS
Tachycardia	9 (9.1)	24 (24.2)	p = 0.007
Hypotension	6 (6.1)	7 (7.1)	NS
Bradycardia	13 (13.1)	4 (4.0)	p = 0.040
Hypoxaemia	14 (14.1)	18 (18.2)	NS
Need for mandible support	1 (1.0)	7 (7.1)	NS
Need for manual ventilation	0 (0.0)	2 (2.0)	NS
Need for intubation	0 (0.0)	1 (1.0)	NS

Hypoxaemia: SpO_2 < 90% for > 30 s. Hypotension: SMP < 90 mmHg or MAP < 60 mmHg. Hypertension: SBP > 180 mmHg or DBP > 100 mmHg. Bradycardia HR < 60 /min. Tachycardia: HR > 100 /min or increase > 20%. Chi-square or Fisher's exact test. NS, not significant (P > 0.05).

Yoon et al 2016[11] studied 50 patients with obstructive sleep apnoea undergoing drug-induced sleep endoscopy, and found the degree of upper airway narrowing aggravated according to the sedation depth for both DEX and propofol. Partial or total obstruction of all the evaluated areas was consistently seen in all patients regardless of the drug. The minimal SpO2 was significantly lower following propofol treatment than following dexmedetomidine treatment (p = 0.004). SpO2 < 90% and SpO2 < 80% were significantly more common during propofol than during dexmedetomidine (p = 0.032 and p < 0.001, respectively).

Ma et al 2012 studied 60 adults with obstructive sleep apnoea. DEX was associated with fewer airway events (events with airway obstruction score of 1, 2 and 3: 29/1/0 vs. 18/9/3; p < 0.01) and less respiratory depression (0 vs. 6 hypoxia events; p < 0.05) compared to propofol.

Post marketing experience

Much of the evidence provided in this application was already available at the time of the 2010 MAA, indeed the MAC and AWAKE studies had already formed the basis for approval of dexmedetomidine for procedural sedation in the USA and other countries at that time. There are many relevant published studies since that time which have contributed to the breath of evidence but have not raised significant new safety concerns.

The cumulative exposure to DEX products Dexdor and Precedex during December 1999 – August 2017 can roughly be estimated to exceed thirteen million patient days. The number of individual case safety reports received from December 1999 to October 2017 is 2921; these reports include altogether 4732 adverse reactions, 2466 of which are serious and 2266 non-serious. The most commonly reported events are hypotension, and bradycardia, presenting about 15 % and 14 % of all the events reported.

Post-marketing AE data from December 1999 to October 2017

PSURs, addendum reports and a line listing were presented in the 2010 MAA for Dexdor. The PSUR cycle is currently annual. There is no systematic method to separate reports related to procedural sedation use of DEX from ICU or other uses.

The number of these reports is 2921, of which 1267 are serious and 1654 are non-serious. They include altogether 4732 adverse reactions, of which 2466 are serious and 2266 non-serious. The most commonly reported events are hypotension reported 707 times and bradycardia reported 660 times. Hypertension has been reported 145 times. Pregnancy has been included in 196 reports, drug administered to a patient of inappropriate age 179 times and off-label use 152 times. Cardiac arrest has been included in 123 reports, pyrexia in 88, drug ineffective in 83, apnoea in 50 and tachycardia in 50 reports. ASTincreased has been reported 62 times, ALT increased 40, vomiting 40, hyperthermia, nausea, drug interaction and agitation 37 times each and respiratory depression 36 times.

The most commonly reported AEs arising from the spontaneous ICSRs are in line with the clinical study AE data and the data described in the Dexdor EU Summary of Product Characteristics sections 4.4 and 4.8. In addition to the safety issues discussed in the proposed Summary of Product Characteristics (SmPC), no new safety signals can be identified from the post-marketing data.

In conclusion post-marketing adverse drug reaction (ADR) reporting has not identified new potential risks of dexmedetomidine of particular relevance to use in procedural sedation.

2.5.11. Discussion on clinical safety

The safety information in the initial MAA is to a large extent applicable to the new indication, and the relatively short duration of procedural sedation also limits the concern for potential safety issues. No deaths were reported in the pivotal studies. No SAEs occurred during study drug infusion while 3 events occurred during the 24 hour follow-up period and 6 events between 24 hours and 30 days follow-up. All the SAEs were assessed as causally not related to the study treatment. However one of the events was hypotension during the recovery period in a vulnerable patient with end-stage renal disease; the conclusion of non-causality seems questionable.

There are some important differences between the existing indication for the sedation of critically ill patients in the ICU, and the proposed indication for procedural sedation that require a different safety perspective. In particular CNS, cardiovascular and respiratory depression that persist after the period

of sedative drug administration are much more important potential safety issues in the procedural sedation setting than in the ICU setting where such things are routine and easily dealt with.

The evaluation of dexmedetomidine safety in procedural sedation is based primarily on the MAC and AWAKE studies, which both included patients with a broad range of comorbidities, including severe systemic disease. Patients were monitored closely for both cardiovascular and respiratory function during and after the study drug infusion. However, the comparison with the comparator group is not with a placebo but with sedation using a protocol directed regimen of midazolam +/- fentanyl. This regimen did not represent “standard of care” as the start of dosing with active sedation was delayed at least until the end of the placebo loading dose infusion, and midazolam was given very slowly in 0.5mg dose increments separated by depth of sedation evaluations. This is not the way midazolam is used for procedural sedation in normal clinical practice and hence a direct comparison of the safety profiles of DEX and standard of care midazolam for procedural sedation is not possible.

The main safety issue for DEX is its well-known cardiovascular effects. Hypotension was reported in 48% and 32% for the DEX 0.5 mcg/kg and 1 mcg/kg loading dose groups respectively in the MAC study (vs. 27% for MID/FEN). This inverse dose-response relationship seems plausible, as vasoconstriction seen at higher concentrations of DEX, would tend to counteract hypotension, despite deeper sedation. The magnitude of the effects of DEX on systolic and diastolic BP, both during the procedure and during recovery, were very substantial. In fit, healthy people, hypotension of the magnitude of the observed mean values is not likely to be of major concern, but in patients with cardiovascular disease there is the potential to cause major adverse cardiovascular events. Furthermore, some patients such as the elderly, hypertensive or frail, may have much greater BP falls than the mean values. It is clear that safe use of DEX will require careful patient selection and the use of vasoconstrictors and chronotropic agents as required. In most cases this should be readily manageable but it presents a significant added complication in anaesthetic management and has the potential to be associated with adverse outcomes.

The exclusion of subjects requiring a spinal or epidural blocks is a limitation of the safety database as there is clearly the potential for an additive effects of DEX and spinal / epidural blockade on sympathetic blockade and hypotension. As DEX has more of a sympatholytic effect than other sedative drugs it seems quite likely that the combination would be inadvisable for routine procedural sedation in patients with spinal or epidural blocks. Appropriate SPC advice to advise against use in such patients should be added to SmPC section 4.4.

DEX is sometimes said in the literature not to cause respiratory depression but this is clearly not true. There are no particular concerns with regard to respiratory depression however, the frequency and extent of which appears to be broadly similar to sedation with midazolam.

Time to recovery was approximately twice as long for DEX as for placebo / midazolam in the MAC study. It is noted that midazolam itself is far from a short acting agent in comparison with for example propofol and remifentanil. This is perhaps not *per se* a safety issue as the patients will be monitored by trained HCPs in a recovery room until they are fit to leave, but it is a major issue for the clinical utility of DEX as an agent for procedural sedation. It seems unlikely for example to be a suitable choice for situations where a reasonably rapid recovery from sedation is desired, such as day case procedures.

The method of dosing is an important focus in this application, for both safety and efficacy. The use of a loading dose is new to the proposed indication for procedural sedation as it is not normally necessary to achieve a rapid effect with DEX in the ICU as patients are normally already sedated. For procedural sedation a rapid onset of effect is required, necessitating use of a loading dose of DEX. A loading dose of 1 mcg/kg infused over 10 minutes is recommended in the proposed SmPC and seems to be reasonably established in non-EU countries where the procedural sedation indication has been

approved for a number of years. The smaller loading dose of 0.5 mcg/kg did not show an improved safety profile in the MAC study; if anything the low DEX 0.5 mcg/kg loading dose seemed to be associated with more AEs than the high DEX 1.0 mcg/kg loading dose. Considering the lack of a clear dose-response relation for adverse events, there seem to be no clear safety grounds for recommending a lower loading dose than 1.0 mcg/kg. There are no available data on the use of loading doses > 1 mcg/kg over 10 minutes in procedural sedation and the MAH concludes that such doses cannot be recommended.

The draft SmPC recommends the maintenance infusion to be generally initiated at 0.6 microgram/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hour, adjusted to achieve the targeted level of sedation. This is as per the MAC study protocol. There are no available data on the use of maintenance DEX infusions >1 mcg/kg/h in procedural sedation and the MAH concludes that such doses cannot be recommended. This is a shame as there seem to be clear indications that a maintenance DEX infusion rate of 1 mcg/kg/h was insufficient to maintain adequate sedation for long procedures (> 1 hour) in a significant proportion of patients in the MAC study.

2.5.12. Conclusions on clinical safety

The safety profile of DEX can be accepted for an indication in procedural sedation. There are some issues, in particular the well-known cardiovascular effects and the slow recovery time but these are manageable in a suitable hospital setting with monitored anaesthetic care and are not considered to be blocking issues.

2.5.13. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted RMP.

The PRAC considered that the RMP version 7.2 (dated 19 June 2018) is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Summary of the safety concerns

Important identified risks	Bradycardia Hypotension Hypertension Hyperglycaemia Withdrawal syndrome
Important potential risks	Atrioventricular block Ischaemic heart disease Cortisol suppression Convulsions Hypothermia Respiratory depression Cardiac arrest Torsade de pointes/QT prolongation Overdose Off-label use
Missing information	Pregnancy

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified Risks		
Bradycardia	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* As described in section 4.2 early signs of bradycardia should be	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	monitored (indication 2.) Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	None
Hypotension	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8.* *PL sections 2, 3, 4* As described in section 4.2 early signs of hypotension should be monitored (indication 2.). The use of a loading dose during procedural sedation may increase the risk for hypotension in the elderly. Contraindication of uncontrolled hypotension in section 4.3 Advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hypertension	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.8* *PL sections 3, 4* As described in section 4.2 early signs of hypertension should be monitored (indication 2.) Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Hyperglycaemia	Routine risk minimisation measures: *SmPC section 4.8* *PL section 4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Withdrawal syndrome	Routine risk minimisation measures: *SmPC sections 4.4, 4.8* *PL section 4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Atrioventricular block	Routine risk minimisation measures: *SmPC sections 4.3, 4.8* *PL sections 2, 4* Contraindication of advanced heart block in section 4.3 Advice that all patients should have continuous cardiac monitoring during Dexdor infusion included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Ischaemic heart disease	Routine risk minimisation measures: *SmPC sections 4.4, 4.8* *PL sections 2, 4* Advice that all patients should have continuous cardiac monitoring during Dexdor infusion included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Cortisol suppression	Routine risk minimisation measures: *SmPC section 5.1* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Convulsions	Routine risk minimisation measures: *SmPC section 4.4* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Hypothermia	Routine risk minimisation measures: Not included in the SmPC Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Respiratory depression	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.5, 4.8, 5.1* *PL section 4* As described in section 4.2 early	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	signs of respiratory depression should be monitored (indication 2.) Advice that respiration should be monitored in non-intubated patients and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Cardiac arrest	Routine risk minimisation measures: *SmPC sections 4.4, 4.8, 4.9* *PL section 2, 4* Advice that all patients should have continuous cardiac monitoring during Dexdor infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Torsade de pointes/QT prolongation	Routine risk minimisation measures: Not included in the SmPC. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Overdose	Routine risk minimisation measures: *SmPC sections 4.2, 4.9, 6.6* Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: None
Off-label use	Routine risk minimisation measures: *SmPC sections 4.1, 4.2, 4.4* *PL section 1 ,3* Indications and instructions for administration included in sections 4.1 and 4.2, respectively Use in only ICU, operating room and during diagnostic procedures emphasised in section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specified follow-up queries for each ICSR Additional pharmacovigilance activities: Study 3005021 (DexDUS)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Pregnancy	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Advice that Dextor should not be used during pregnancy unless the clinical condition of the woman require treatment with dexmedetomidine included in section 4.6 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections X, Y, Z of the SmPC have been updated. <Particularly, a new warning with regard to XXX has been added to the product information.> The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Dexmetomidine Ever Pharma The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The objective of procedural sedation is to provide comfort and relief of anxiety during diagnostic, surgical and other procedures such as endoscopy, wound care, reduction of fractures and dislocations, radiological examinations, vascular access procedures, endovascular procedures, minor surgery, and cardioversion. It follows that the target population for procedural sedation in general is very diverse, spanning the entire age spectrum and with variable severity of complicating conditions and comorbidity. The duration of a diagnostic/surgical procedure may vary from minutes to hours. Usually the objective is to achieve a minimal reduction in conscious level but no loss of consciousness. Patients undergoing procedural sedation are expected to be able to breathe independently, and to maintain

their airway without intervention. Depending on the type of procedure, analgesia may be a supplementary requirement. In some situations amnesia is a desirable additional effect of sedation, especially for procedures that can be unpleasant but need to be repeated regularly (e.g. GI endoscopy).

Procedural sedation is not always restricted to an environment where full anaesthetic equipment is available (e.g. operating theatre) but may take place also in other settings, such as in a radiology department or an endoscopy clinic. This is in contrast to the currently approved indication for sedation of adult Intensive Care Unit patients. Procedural sedation may be administered by a specialist anaesthetist, by a non-anaesthetist physician, or by a non-medically qualified healthcare professional.

Procedural sedation provides different safety challenges compared to ICU sedation. Patients are not intubated and so have an unsecured airway. The onset of effect needs to be rapid, sedation may be conducted under less-stringent monitoring conditions, sometimes by non-anaesthetists, and patients may be discharged home soon afterwards, depending on the type of procedure concerned. It is a pre-requisite, supported by a number of guidelines, that IV sedation with agents like dexmedetomidine is conducted only in adequate facilities that have equipment for monitoring, suction, oxygen supplementation, ventilatory support and resuscitation. Sedation should only be performed by a suitably trained health care professional, not involved in the surgery or procedure, and not by a lone operator.

3.1.2. Available therapies and unmet medical need

Respiratory depression is the major undesirable effect of most agents (benzodiazepines such as midazolam, IV anaesthetic such as propofol, short acting opioids such as fentanyl) currently used for procedural sedation. Over sedation with benzodiazepines and opioids leading to respiratory depression has been reported to be the most common cause of death or permanent brain damage in this clinical situation (especially when operator administered).

Propofol has undesirable side effects of hypotension, apnoea, airway obstruction, and consequent oxygen desaturation, especially when co-administered with an opioid. Propofol is only suitable for use by an anaesthetist. Opioids are the agents of choice for treating pain, and short acting opioids may be an agent of choice for certain procedures such as awake fibreoptic intubation, where they have the important advantage of attenuating airway reflexes. However opioids used as the sole sedative agent are liable to cause respiratory depression so again are suitable for use only by an anaesthetist for this purpose.

A short acting benzodiazepines, in particular midazolam, is widely considered to be the agent of choice for procedural sedation that is administered by a healthcare professional other than an anaesthetist. This is because the therapeutic index is less narrow in terms of respiratory depression. As benzodiazepines do not have analgesic effects, supplementation with an opioid is required for painful procedures. Respiratory depression remains an important complication of procedural sedation with a benzodiazepine.

Ketamine can be used as a sole agent or as an adjunct (especially in combination with a benzodiazepine), and differs from the aforementioned agents in several aspects, including its dissociative CNS effects and analgesic properties.

The use of DEX for awake fibreoptic intubation in a patient with a potentially difficult airway was specifically studied in a separate trial. This is an extremely stimulating procedure that may be associated with large haemodynamic changes. To attenuate this response, blunting of the airway

reflexes is required without losing the cooperation of the patient. A successful awake fibreoptic intubation requires an anaesthetist experienced in this technique, attenuation of airway reflexes (by topical anaesthesia of the airway +/- systemic drugs), and a sedated yet cooperative patient. The most common complications of this procedure are hypoxia and gastric content aspiration.

It can be agreed that there is an unmet need for a sedative agent for procedural sedation that causes less respiratory depression than currently available agents, especially in high-risk patients (difficult airway, obese, very sick, elderly).

3.1.3. Main clinical studies

The evidence of efficacy for the proposed new indication comes primarily from two phase III randomised, double-blind, placebo-controlled, multicentre studies MAC (2005-005) and AWAKE (2005-006), in in non-intubated patients requiring sedation. These two trials are supplemented with an extended review and analysis of literature. The MAC and AWAKE studies are the same studies that another company, Hospira, used to obtain approval of Precedex for the same indication in the USA in 2008 and in a number of other countries. The clinical study reports (CSRs) of these studies were submitted in the 2010 MAA for Dexdor in ICU sedation, but were not discussed in detail at that time since an indication for procedural/awake sedation in non-intubated patients was not sought in that application. Both of these studies are now presented in detail to support this variation application to add the indication for procedural/awake sedation in non-intubated patients.

The MAC study (2005-005) evaluated dexmedetomidine for sedation under the control of an anaesthetist in 326 patients undergoing surgery under local or regional anaesthesia. It was conducted at 26 sites in the USA and enrolled a broad range of patients scheduled for a variety of elective surgical procedures including orthopaedic, ophthalmic, plastic, vascular, breast biopsies and excision of lesions. Subjects received a loading dose of study drug administered over 10 minutes (DEX 0.5 mcg/kg, DEX 1 mcg/kg, or placebo). The maintenance infusion was then initiated at DEX 0.6 mcg/kg/hr for all subjects randomized to receive DEX; and PBO for all subjects randomized to receive PBO. It could be titrated according to clinical response within the range 0.2 to 1.0 mcg/kg/hr. After 15 minutes of infusion of randomised study drug (DEX or PBO) “rescue” midazolam (MDZ) could be given if necessary, in incremental 0.5 mg IV doses, to achieve the necessary level of sedation. Fentanyl could also be administered to provide analgesia. The primary endpoint was the percentage of subjects not requiring MDZ for rescue sedation based on achieving and/or maintaining an OAA/S sedation score $\leqslant$ 4.

The AWAKE study (2005-006) evaluated dexmedetomidine for awake fibreoptic oral or nasal intubation prior to a surgical or diagnostic procedure in 105 patients expected to be difficult to intubate. It was conducted at 17 sites in the USA. Subjects received a loading dose of study drug administered over 10 minutes (DEX 1 mcg/kg, or placebo). The maintenance infusion was then initiated at DEX 0.7 mcg/kg/hr for all subjects randomized to receive DEX; and PBO for all subjects randomized to receive PBO. It could NOT be titrated according to clinical response. Instead, after 15 minutes of infusion of randomised study drug (DEX or PBO) “rescue” midazolam, in incremental 0.5 mg IV doses, could be given if necessary to achieve the necessary level of sedation. Fentanyl could also be administered to provide analgesia. The primary endpoint was the percentage of subjects requiring rescue MDZ to achieve and/or maintain proper sedation levels (RSS score $\geqslant$2 throughout the study drug infusion.

3.2. Favourable effects

MAC study

In the primary efficacy analysis, the percentage of subjects not requiring MDZ for rescue sedation based on achieving and/or maintaining an OAA/S ≤4 throughout the study drug infusion period was 40.3% for the DEX 0.5 mcg/kg group, 54.3% for the DEX 1.0 mcg/kg and 3.2% for the PBO group. The p values for the comparisons of active vs. PBO were <0.001 for both DEX groups.

Results for key secondary analyses are presented below for the DEX 0.5 mcg/kg group, DEX 1.0 mcg/kg and the PBO groups respectively, with p values for the DEX vs. PBO comparisons).

Mean total dose of rescue MDZ – 1.4mg / 0.9mg / 4.1mg (p <0.001 for both DEX groups)

Median time to receive 1st dose of MDZ – 40 mins / 114 mins / 20 mins (p <0.001 for both DEX groups)

Median time to recovery and readiness for discharge from monitored recovery room – 29 mins / 25 mins / 14 mins (p = 0.068 and p = 0.076 for 0.5 and 1.0 DEX groups respectively).

% requiring fentanyl for analgesia during infusion– 59% / 43% / 89% (p <0.001 for both DEX groups)

% requiring fentanyl for analgesia post procedure 3.7% / 3.9% / 9.5% (NS for both DEX groups)

AWAKE study

In the primary efficacy analysis, the percentage of subjects requiring rescue MDZ to achieve and/or maintain proper sedation levels (RSS score ≥2 throughout the study drug infusion was 47.3% for the DEX group and 86.0% for the PBO group (p <0.001).

Results for key secondary analyses are presented below for the DEX group and the PBO groups respectively, with p values for the DEX vs. PBO comparisons.

Median Ramsay Sedation Scale (RSS) scores, assessed 15 minutes after starting study drug 2.1 vs. 1.7 (p <0.001). The RSS is an ordinal scale of 1 to 6 where low score indicates less sedation.

Mean total dose of rescue MDZ – 1.07 mg / 2.85mg (p <0.001)

Anaesthetist assessments on a 0 to 10 point VAS with low scores favourable (DEX group)

- Ease of intubation 3.16
- Haemodynamic stability 1.91
- Subject co-operation 2.53

Published studies

Some supportive evidence is also provided from published studies and a recent systematic review (without meta-analysis) of RCTs. The data were variable due to the methodological heterogeneity of the trials (clinical situations, dose protocols etc) but in general evidence of sedation and pain relief was broadly consistent with the findings of the MAC and AWAKE trials.

3.3. Uncertainties and limitations about favourable effects

The design of the MAC and AWAKE phase III trials, using placebo (saline) in the control arm with midazolam as rescue medication to ensure adequate sedation could be achieved for all patients. This apparently was agreed between a previous MAH for DEX (Hospira) and the FDA. However the design of these trials lacks the possibility to compare sedation with Dexdor to that achieved with a standard agent such as midazolam. This is a major weakness in the data package.

Demonstrating superiority to placebo is considered inadequate for the purpose of this application. It is necessary to establish that DEX has sufficient efficacy for it to be recommended as a valid therapeutic option for the proposed clinical use. There is no requirement for it to be superior or even equivalent to existing methods (e.g. midazolam) but the MAH is required to demonstrate that DEX has the efficacy expected of a sedative agent intended for procedural sedation, preferably as a sole agent, supplemented as necessary with an opioid analgesic.

As such this pivotal trial is conceptually fundamentally flawed. The design does not allow for a direct comparison of the DEX regimens with a standard sedation method (midazolam). Some comparisons can be made with the PBO control group, which received sedation with midazolam but only after at least 15 minutes of placebo infusion and at a much slower rate of administration (0.5mg incremental doses) than would be normal in clinical practice. The differences between DEX and placebo treatment groups in the dose of administered midazolam rescue medication seem small. It seems likely that the design of the study and the constraints of the trial protocol may have led to relative under-dosing with midazolam in the PBO group. Furthermore, the study would have been functionally unblinded to a very substantial extent. For these multiple reasons it is considered unreliable to make comparisons between the DEX and PBO treatment groups, except for the very obvious and rather unhelpful conclusion that dexmedetomidine has more sedative effect than normal saline.

About half of patients in the DEX groups in both trials required rescue midazolam to achieve the desired level of sedation. This does not inspire confidence that DEX can reliably achieve the desired effect as a procedural sedative, but it is not clear to what extent this might be the case in clinical practice. Certainly some patients in the MAC trial were given rescue midazolam instead of attempting to up-titrate the infusion rate of DEX.

The trial design also makes it difficult to scrutinise claims that DEX has an advantage over other available sedation methods in terms of better ability of the sedated patient to co-operate with verbal instructions.

The review of the published literature cannot fully address these uncertainties.

3.4. Unfavourable effects

No unexpected safety issues have been identified from the evaluation of the proposed new indication. The relatively short duration of procedural sedation also limits the concern for potential safety issues.

The percentage of patients who had AEs was 84% in the combined DEX groups compared to 72% for placebo / rescue. For treatment related AEs the numbers were 53% vs. 28%. No deaths were reported in the pivotal studies. No SAEs occurred during study drug infusion, and while three events occurred during the 24 hour follow-up period and six events between 24 hours and 30 days follow-up, all were assessed as causally not related to the study treatment.

Hypotension was an extremely common reported AEs, as expected from the pharmacological properties and known safety profile of DEX. Hypotension was defined as SBP < 80 mmHg OR ≤30% lower than pre-study drug infusion values OR DBP < 50 mmHg. Bradycardia (HR < 40 bpm OR ≤ 30% lower than pre-study drug infusion values) was also common.

The incidences of respiratory depression in the MAC study were 37% (DEX 0.5mcg/kg loading), 34% (DEX 1.0mcg/kg loading) and 33% (placebo / midazolam).

The median times to recovery and readiness for discharge from the post anaesthetic care unit in the MAC study were 29 minutes (DEX 0.5mcg/kg loading), 25 minutes (DEX 1.0mcg/kg loading) and 14 minutes (placebo / midazolam).

3.5. Uncertainties and limitations about unfavourable effects

The evaluation of dexmedetomidine safety in procedural sedation is based primarily on the MAC and AWAKE studies, which both included patients with a broad range of comorbidities, including severe systemic disease. Patients were monitored closely for both cardiovascular and respiratory function during and after the study drug infusion. However, the comparison with the comparator group is not with a placebo but with sedation using a protocol directed regimen of midazolam +/- fentanyl. This regimen did not represent “standard of care” as the start of dosing with active sedation was delayed at least until the end of the placebo loading dose infusion, and midazolam was given very slowly in 0.5mg dose increments separated by depth of sedation evaluations. This is not the way midazolam is used for procedural sedation in normal clinical practice and hence a direct comparison of the safety profiles of DEX and standard of care midazolam for procedural sedation is not possible.

It is expected that patient characteristics such as age, cardiovascular comorbidity, and/or concomitant baseline medication could be relevant risk factors, but the data does not identify that. Elderly patients were included in the studies but they are relatively few. The number of patients was insufficient for detailed analyses of subgroups.

Although all SAEs were assessed as causally not related to the study treatment, one was hypotension during the recovery period (in a vulnerable patient with end-stage renal disease) so the determination of this event as not causally related to DEX seems questionable.

An important practical aspect of procedural sedation is rapid recovery, allowing as early discharge from PACU and hospital (e.g. following day-case surgery) as possible. The data indicate that DEX is expected to have a prolonged recovery period compared to e.g. propofol, due to its pharmacokinetic and pharmacodynamic properties.

The exclusion of subjects requiring a spinal or epidural blocks is a limitation of the safety database as there is clearly the potential for an additive effects of DEX and spinal / epidural blockade on sympathetic blockade and hypotension. As DEX has more of a sympatholytic effect than other sedative drugs it seems quite likely that the combination would be inadvisable for routine procedural sedation in patients with spinal or epidural blocks. Appropriate SPC advice to advise against use in such patients has been added to SmPC section 4.4.

There is not a clear dose-response relation between different doses and adverse reactions. While DEX consistently lowered blood pressure there was no apparent dose-response with the two dosage levels used in the MAC study. The incidence of hypotension during the early high-dose infusion period did not appear to be related to the ASA status, and thus the overall health status of the patients. There was a tendency that hypertension increased with age, but apparently with little difference between the dose

groups. The lack of a clear dose-response relation for adverse events raises further questions regarding the dosing regimen and not well described PK/PD relation in the submitted data.

There are no available data on the use of loading doses > 1 mcg/kg over 10 minutes or on the use of maintenance DEX infusions >1 mcg/kg/h in procedural sedation. The MAH concludes that such doses therefore cannot be recommended. This is a shame as there seem to be clear indications that a maintenance DEX infusion rate of 1 mcg/kg/h was insufficient to maintain adequate sedation for long procedures (> 1 hour) in a significant proportion of patients in the MAC study. The MAH was asked review any available post-marketing or published data in patients who received a higher maintenance infusion rate than recommended in the current draft SmPC and discuss the possibility of using higher doses where needed. The responses were satisfactory. It is agreed that there are insufficient data to support higher loading or maintenance dose than those proposed. Instead there is a recommendation to give additional analgesia or sedatives (e.g. opioids, midazolam or propofol) if increased depth of sedation is necessary.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

General procedural sedation (MAC study)

It is not in doubt that DEX was more effective than placebo in this trial. That was very obviously going to be the case as DEX is a currently approved sedative drug. The differences between DEX and placebo groups in the dose of rescue MDZ needed were modest.

It seems unimpressive that even in the high dose DEX group, half of the patients required rescue midazolam. The dose regimen advised in the SPC is the same as that in the trial protocol. This posology seems to be insufficient in about half of the patients. The need for rescue midazolam occurred late (median time 114 minutes after start of infusion). This seems to suggest that a higher maintenance infusion rate might be required in some patients to maintain adequate sedation levels for long procedures. Unfortunately there are no safety or efficacy data with a higher maintenance infusion rate.

It misleading to state (as the MAH does) that there were no significant differences between groups in the time to recovery and readiness for discharge from the PACU. Time to recovery was approximately twice as long for DEX as for the PBO group. For the low dose and high dose DEX groups separately the difference from placebo both just fail to reach statistical significance ($p = 0.068$ and $p = 0.076$ respectively) but for the combined DEX groups the difference would certainly be highly statistically and clinically significant.

Overall however it can be concluded that DEX was effective as an agent for procedural sedation, at least for short procedures and with the possibility to supplement with midazolam. The main concerns and uncertainties in the first round related to dose. The need for supplemental midazolam after one hour or longer in about half of patients dosed in accordance with the draft SPC section 4.2 seems to suggest that a higher upper limit for the infusion rate may be necessary. This concern was raised in the first LoOI and was satisfactorily addressed in the MAH's responses, in particular by adding a statement that: "Additional analgesia or sedatives (e.g. opioids or midazolam, propofol) are recommended in case of painful procedures or if increased depth of sedation is necessary." This is satisfactory and addresses the concern that DEX alone was not sufficient in a proportion of cases.

Using two drugs to achieve sedation when one could suffice (i.e. midazolam) is not ideal and might unnecessary complexity, but if there is a good reason to choose DEX, there is no reason why this plus a small amount of supplementary opioid, midazolam or propofol would not be a satisfactory sedation method.

An analgesic effect of DEX was quite convincingly seen although in practice the opioid sparing effect is rather unimportant. Otherwise the design of the trial does not allow for a meaningful comparison with midazolam for aspects such as quality of sedation with regard to maintenance of communication.

DEX caused substantial adverse cardiovascular effects, in particular hypotension & bradycardia. These are manageable by an anaesthetist in a fully monitored environment but are likely to present an unacceptable hazard for procedural sedation administered by a non-anaesthetist. The draft SmPC states “Dexdor should be administered only by health care professionals skilled in the anaesthetic management of patients in the operating room or during diagnostic procedures”. Crucially this restriction refers to “anaesthetic management” which seem sufficient to restrict use to appropriately skilled personnel. In some countries “nurse anaesthetists” administer anaesthetics under the supervision of a medically qualified anaesthetist and in such situations the nurse anaesthetist would have the necessary competencies to administer Dexdor for procedural sedation.

AWAKE study

The study has achieved statistical significance on the primary endpoint but the conclusion that DEX produced more sedation than placebo is no basis for concluding that it is adequately effective for the studied clinical use. In fact the opposite seems to be true for many patients. About half in the DEX group required rescue MDZ to achieve a very light degree of sedation (RSS score of 2, “co-operative, oriented and tranquil”). The difference between DEX and PBO groups of 0.4 points on the 6 point RSS seems rather small. The adequacy of the effect of the DEX loading dose in achieving procedural sedation for awake fibreoptic intubation is therefore questioned.

A big problem for this trial is the fixed dose of both loading dose and maintenance infusion of DEX. Sedative drugs have a dose – response for both their primary PD activity and their undesirable effects, in particular cardiovascular and respiratory depression. DEX is no exception. They therefore need to be titrated according to individual clinical response. The AWAKE trial is conceptually flawed because if tells us very little about whether DEX can reliably provide sedation as the sole agent for awake fibreoptic intubation. A failure rate of 47% as seen in this study seems unacceptable. It is to be expected that a higher success rate could be achieved with a more appropriate flexible dose regimen that allowed for higher infusion rates as required to achieve adequate sedation. Unfortunately, the design of this trial does not enable us to get any information on what the range of those dose requirements might be. Importantly, it also does not establish whether DEX as a single agent can reliably achieve the necessary sedation with acceptable safety. It might be that at the higher doses of DEX necessary to achieve adequate sedation, safety might become more problematic. For awake fibreoptic intubation the main concern would be respiratory depression before the airway could be secured.

In conclusion in the first round, CHMP concluded that the AWAKE trial does not provide sufficient evidence of efficacy for uses as a sole agent for sedation for awake fibreoptic intubation. This was raised as a Major Objection in the first LoOI but was satisfactorily addressed in the MAH’s responses. In particular, the MAH proposed to add a statement that: “Additional analgesia or sedatives (e.g. opioids or midazolam, propofol) are recommended in case of painful procedures or if increased depth of sedation is necessary.” This is satisfactory and addresses the concern that DEX alone was not sufficient in a proportion of cases. As with the wider procedural sedation indication, using two drugs to achieve sedation when one could suffice (i.e. midazolam) is not ideal and might unnecessary

complexity, but if there is a good reason to choose DEX, there is no reason why this plus a small amount of supplementary opioids, midazolam or propofol would not be a satisfactory sedation method.

Safety

The safety information in the initial MAA is to a large extent applicable to the new indication, but there are some important differences between the existing indication for the sedation of critically ill patients in the ICU, and the proposed indication for procedural sedation, that require a different safety perspective. In particular CNS, cardiovascular and respiratory depression that persist after the period of sedative drug administration are much more important potential safety issues in the procedural sedation setting than in the ICU setting where such things are routine and easily dealt with.

The main safety issue for DEX is its well known cardiovascular effects. Hypotension was reported in 48% and 32% for the DEX 0.5 mcg/kg and 1 mcg/kg loading dose groups respectively in the MAC study (vs. 27% for MID/FEN). This inverse dose-response relationship seems plausible, as vasoconstriction seen at higher concentrations of DEX, would tend to counteract hypotension, despite deeper sedation. The magnitude of the effects of DEX on systolic and diastolic BP, both during the procedure and during recovery, were very substantial. In fit, healthy people, hypotension of the magnitude of the observed mean values is not likely to be of major concern, but in patients with cardiovascular disease there is the potential to cause major adverse cardiovascular events. Furthermore, some patients such as the elderly, hypertensive or frail, may have much greater BP falls than the mean values. It is clear that safe use of DEX will require careful patient selection and the use of vasoconstrictors and chronotropic agents as required. In most cases this should be readily manageable but it presents a significant added complication in anaesthetic management and has the potential to be associated with adverse outcomes.

DEX is sometimes said in the literature not to cause respiratory depression but this is clearly not true. There are no particular concerns with regard to respiratory depression however, the frequency and extent of which appears to be broadly similar to sedation with midazolam.

Time to recovery is seen to be approximately twice as long for DEX as for placebo / midazolam in the MAC study. It is noted that midazolam itself is far from a short acting agent in comparison with for example propofol and remifentanil. This is not *per se* a safety issue as the patients will be monitored by trained HCPs in a recovery room until they are fit to leave, but it is a major issue for the clinical utility of DEX as an agent for procedural sedation. It seems unlikely for example to be a suitable choice for situations where a reasonably rapid recovery from sedation is desired, such as day case procedures.

The method of dosing is an important focus in this application, for both safety and efficacy. The use of a loading dose is new to the proposed indication for procedural sedation as it is not normally necessary to achieve a rapid effect with DEX in the ICU as patients are normally already sedated. For procedural sedation a rapid onset of effect is required, necessitating use of a loading dose of DEX. A loading dose of 1 mcg/kg infused over 10 minutes is recommended in the proposed SmPC and seems to be reasonably established in non-EU countries where the procedural sedation indication has been approved for a number of years. The smaller loading dose of 0.5 mcg/kg did not show an improved safety profile in the MAC study; if anything the low DEX 0.5 mcg/kg loading dose seemed to be associated with more AEs than the high DEX 1.0 mcg/kg loading dose. There seem to be no clear safety grounds for recommending a lower loading dose than 1.0 mcg/kg.

One patient who received DEX, fentanyl 100 mcg and no rescue MDZ, discontinued the trial due to an infusion site reaction. ISRs are not listed in section 4.8 of the Dexdor SPC and there were no other cases reported in the trials so a discontinuation for this reason is curious. The narrative summary gives no useful further information ("hives at the IV insertion site"). The MAH was asked to discuss whether infusion site reactions should be added to the SPC section 4.8, considering also any relevant post marketing data. The response was satisfactory and it is agreed that no SPC wording is necessary.

3.6.2. Balance of benefits and risks

In the MAC study DEX, at the doses recommended in the draft SmPC, was shown to be effective for procedural sedation although a significant percentage of patients required supplementary midazolam to achieve the necessary depth of sedation. It cannot be concluded that DEX achieves adequate sedation reliably as a sole agent and the frequent need to administer a second agent is not entirely satisfactory, but is not a deal breaker. It is unknown whether this proportion might be different in routine clinical practice compared to the clinical trial setting which set some rather rigid rules for DEX dose adjustment and midazolam administration. No benefit in terms of efficacy over midazolam based sedation could be concluded. An opioid sparing effect was seen, which could be advantageous in certain clinical situations e.g. in patients taking naltrexone for alcohol and/or drug misuse.

The most important safety issues concern the well known cardiovascular effects and the slow recovery time. However these are considered manageable in a suitable hospital setting with monitored anaesthetic care and are not considered to be blocking issues. The safety profile of DEX can be accepted as acceptable for an indication in procedural sedation, subject to the restriction to administration only by health care professionals skilled in anaesthetic management.

Based on the presented data, dexmedetomidine is an acceptably safe and efficacious alternative for the provision of sedation during surgery and diagnostic or other procedures provided it is used at the proposed dose and under the clinical conditions described in the proposed SmPC, with a recommendation to use additional analgesia or sedatives (e.g. opioids, midazolam or propofol) in case of painful procedures or if increased depth of sedation is necessary.

3.7. Conclusions

The overall B/R of Dexdor is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include "For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation" for Dexdor;
as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.7, 4.8 and 5.1 of the SmPC are updated. The Package

Leaflet is updated in accordance. The RMP is updated to version 7.2.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include "For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation" for Dexdor;
as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.7, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 7.2.

Summary

Please refer to the Scientific Discussion Dexdor EMEA/H/C/002268/II/0026.